CARCINOMA OF THE THYROID GLAND

Carcinoma of the Thyroid Gland

A Clinical and Pathologic Study of 293 Patients at the University of California Hospital

By

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CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • U. S. A.

CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue, Springfield, Illinois, U S A.

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD, OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

Library of Congress Catalog Card Number 59-11900

Printed in the United States of America

To the late
Mayo H. Soley, M. D.

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FOREWORD

DURING the last 14 years, systematic clinical and pathologic studies of patients with several forms of thyroid disease have been made at the University of California Hospital. These earlier correlative studies were done in collaboration with Dr. Morris E. Dailey and the late Dr. Mayo H Soley.

This report on thyroid carcinoma was not intended to be a complete, definitive review of the disease, but rather a clinical and pathologic report of patients treated at the University of California Hospital from 1920-1954, and was designed to study the natural history of thyroid carcinoma as observed in this group of patients.

The majority of patients were from the private surgical services of the University of California Hospital, and I am indebted to Drs. H. Glenn Bell, Leon Goldman, Orville F Grimes, Horace J. McCorkle, Henry H Searls and Robertson Ward for the privilege of reviewing the clinical records of their patients

For many years, the late Mrs. Eleanor Wells was the secretary in the Department of Surgery and conducted the follow-up of these patients This study would not have been possible without the excellent follow-up data compiled by Mrs Wells.

In the preliminary and relatively uninteresting phases of this study, my old friends, Dr Morris E Dailey and Dr William H. Rustad aided tremendously in organizing the plan of study, and it is regrettable that they were unable to continue their interests in this study of thyroid carcinoma.

The statistical studies which form a large part of this report were possible through the valuable cooperation of Dr Calvin Zippin, Director of the General Tumor Registry of the University of California School of Medicine Miss Janet Hitchcock of the General Tumor Registry assisted in the calculations to determine significance of the data

Grateful acknowledgement is made to Mr Hal Strong who is a photographic artist and who prepared the photomicrographs, and to Dr Bruno Gerstl, Chief of the Laboratory at the Oakland

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Veterans Administration Hospital for his cooperation in use of his photographic facilities.

Miss Helen Gee who is an artist in illustration prepared the many tables necessary in this report. Miss Lucy Lawrence, Editor of the Agriculture Publications of the University of California, removed dangling participles and other imperfections from the manuscript. Dr. Jackson T. Crane of the Department of Pathology and Dr. William H. Rustad of the Department of Surgery kindly reviewed the manuscript, and made many valuable suggestions in its final preparation.

I am especially grateful to Mrs. Jean Friedlander for her aid in this study and indeed in all our studies of thyroid disease. Without Mrs Friedlander's personal interest in and knowledge of the patients attending the Thyroid Clinic for many years, compiling the data for this study would have been an almost impossible chore.

San Francisco, California STUART LINDSAY, M. D

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Chapter I

INTRODUCTION

CARCINOMA of the thyroid gland is one of the most intriguing of human cancers Interest in the disease is reflected in the extensive literature devoted to its various aspects. Although its prevalence and incidence are low when compared with those of other types of human cancer, thyroid carcinoma has a wider spectrum of patterns of growth and of varying biologic characteristics than do most other malignant human neoplasms.

This disease is unique in many respects. (a) the differences in incidence and types in different geographic areas, (b) the frequently observed disparity between the histologic pattern of thyroid cancer and its biologic activity — an attribute first described by Cohnheim in 1876 (1); (c) the unusually long course of the majority of thyroid cancers as compared with those of neoplasms originating in other sites; (d) the clinical and experimental evidence that thyroid cancer is probably subject to biologic control by the organism, and that such control is likely endocrine in nature Indeed, clinical and experimental evidence both suggest that endocrine stimulation is etiologic in this disease, and that the malignant process may be controlled by inhibiting this endocrine stimulation.

A precise knowledge of the natural history of thyroid carcinoma, including the expected or possible natural course of the disease either with or without specific therapy, is needed in order to plan rational prevention and control.

It is not possible to study thyroid carcinoma in the human being in the same way as in the experimental animal because, with the human, therapy of some sort is almost always administered during the course of the disease No group of untreated patients with thyroid carcinoma is available for study. It is evident, therefore, that both therapy and the biologic warfare between the cancer and the patient determine the final outcome Fortunately, surgical therapy, often repeated, provides tissue from the primary lesion

and metastases for study — a technique usually not feasible in the experimental animal.

The study was designed to gain further detailed knowledge of the natural history of thyroid carcinoma. The report stresses the initial clinical manifestations of the disease, its origins in normal or pathologic thyroid tissues, its manner and rate of growth and dissemination within the thyroid gland, its routes of dissemination from the gland and the sites of metastatic localization, and its course and duration in relation to the three major histologic patterns characteristic of thyroid carcinoma.

This report also particularly emphasizes patient-survival data, calculated both from the time of onset of the disease and from the time of initial diagnosis and operation. Survival data in relation to specific clinical and pathologic features of the disease have clarified a number of important questions regading therapy and prognosis, questions which must be answered before attacking this malignant neoplasm with confidence.

No attempt has been made to review the literature on thyroid neoplasms extensively. The reader is referred to the yearly bibliography of thyroid disease compiled by Dr. Lindon Seed of Chicago.

Definition of Thyroid Carcinoma

For the purposes of this report, thyroid carcinoma is defined as an abnormal, proliferating growth of thyroid epithelium, as a rule locally infiltrating the thyroid glandular parenchyma, and eventually extending outside the thyroid gland, either by direct invasion or by lymphatic or vascular dissemination. On the basis of past experience and the cytologic and histologic patterns, relatively localized lesions were classified as malignant when patterns were similar to or identical with those of neoplasms which had obvious invasive or disseminating characteristics.

A variety of pathologic processes in the thyroid gland may be mistaken for malignant lesions on the basis of cytologic and histologic criteria (2). These include fibrosis, thyroid epithelial proliferation, and cytologic abnormalities, including pleomorphism and apparent hyperchromatism, features frequently observed in Hashimoto disease. These bizarre processes are, however, rather easily differentiated from thyroid cancer by the pathologist, as a rule with much less difficulty than believed by some surgeons (3).

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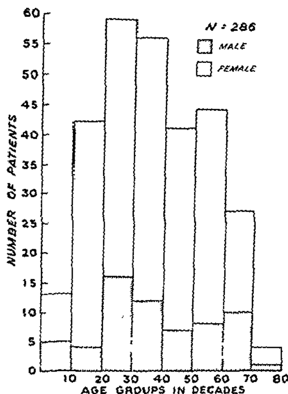
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to follow-up. In the past few months (1958) one patient with follicular carcinoma has returned with a metastatic vertebral lesion, and a second patient has died of papillary thyroid carcinoma 20 years following operation.

Age and Sex Incidence

In Table 4, the distribution of ages at onset of goiter is bimodal, with peaks in the third and sixth decades. In seven of the patients,

Table 4



either no goiter was present or the age of onset of goiter was unknown Table 5 shows a similar age distribution calculated from the age at the estimated onset of carcinoma A bimodal distribution is also observed, with peaks in the fourth and sixth decades. A unimodal distribution of ages is shown in Table 6, calculated from the ages of the patients at the time of diagnosis and operation. From the data in Tables 4, 5, and 6, it is apparent that thyroid

Table 6

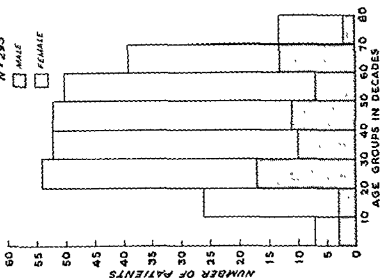
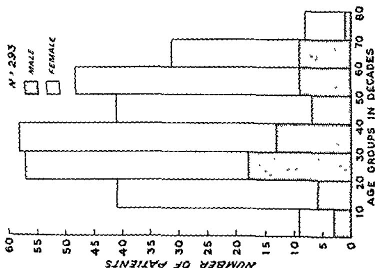


Table 5



carcinoma, usually with goiter, may originate at any time during life, but that its incidence is highest in the third, fourth, and sixth decades. When calculated at the time of operation, however, there is a slightly higher incidence in the third.

Tables 7 and 8 show the incidence of papillary, follicular, and anaplastic carcinoma beginning under and over the age of 40 years, in males and females. There are no significant differences in incidence between males and females with each type of thyroid carcinoma under 40 years of age (papillary, $X_2 = 0.03$; follicular, $X_2 = 0.46$; and anaplastic, $X_2 = 0.296$ with 1 df). The same is true for males and females over 40 years of age (papillary, $X_2 = 0.3$; follicular, $X_2 = 0.23$, and anaplastic, $X_2 = 0.34$ with 1 df).

Table 7

INCIDENCE OF THYROID CARCINOMA IN MALES AND FEMALES UNDER 40 YEARS OF AGE

	Male	*Female*	*Total*
PAPILLARY	30	88	M 45
			F 135
FOLLICULAR	11	34	M 18
			F 70
ANAPLASTIC	0	2	M 3
			F 22
			293

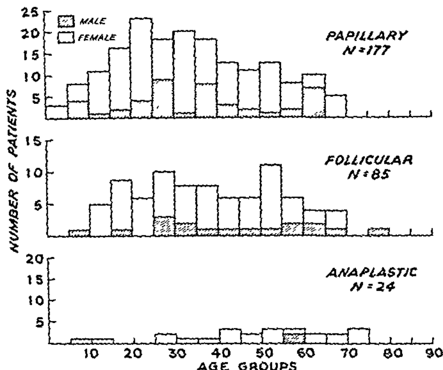
Table 8

INCIDENCE OF THYROID CARCINOMA IN MALES AND FEMALES OVER 40 YEARS OF AGE

	Male	*Female*	*Total*
PAPILLARY	15	47	M 45
			F 135
FOLLICULAR	7	36	M 18
			F 70
ANAPLASTIC	3	20	M 3
			F 22
			293

In the three major types of thyroid carcinoma, there is a wide distribution of age at onset of goiter (Table 9). A slightly higher age incidence is found in the second, third, and fourth decades with

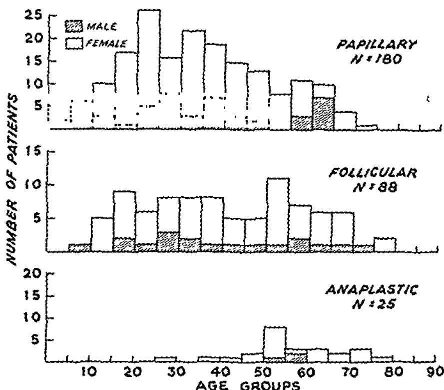
Table 9



papillary carcinoma, and in the sixth decade with follicular carcinoma Patients with anaplastic carcinoma show a wide distribution of ages at onset of goiter.

The age incidence at the estimated onset of the three major types of thyroid carcinoma is shown in Table 10 Peaks of incidence of papillary carcinoma are noted in the 20-25, 30-35 and the 55-60 year groups Follicular carcinoma shows peak incidences in the 15-20 and 50-55 year periods. The age of onset of anaplastic carcinoma is significantly later, with the majority apparently beginning after 50 Only three probably began before the age of 45. Comparison of the distribution of the ages of onset of goiter (Table 9) and the age of onset of cancer (Table 10) clearly shows that the patients with anaplastic carcinoma may have had long-standing goiter prior to the development of obvious carcinoma. In the papil-

Table 10

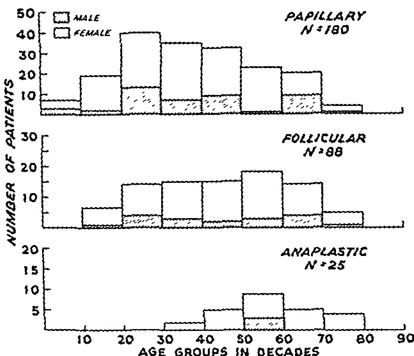


lary and follicular groups, on the other hand, the distribution of ages of onset of goiter is quite similar to that of ages of onset of the carcinoma — evidence suggesting that these goiters are malignant from their onset. Table 11 shows a unimodal distribution of ages at the time of operation for patients with papillary, follicular, and anaplastic carcinoma. Patients with anaplastic carcinoma are in significantly older age groups.

The sex incidence of all thyroid carcinoma and of the three major groups is given in Tables 4, 5, 6, 9, 10, and 11. Although carcinoma of the thyroid gland is predominately a disease of females, its incidence is less than that observed for females in other thyroid disorders, such as diffuse toxic goiter, nodular goiter, and Hashimoto disease. It is generally believed that the higher incidence of most thyroid disease in females results from greater thyroid activity

Table 11

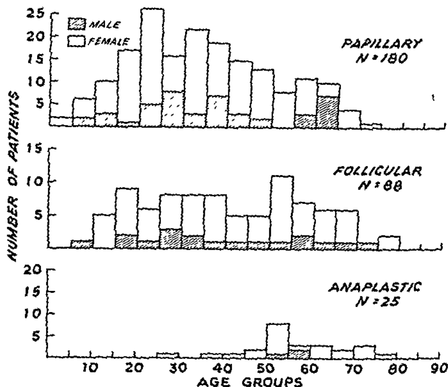
AGE AND SEX INCIDENCE OF THYROID CARCINOMA
AGE AT OPERATION



occasioned by the menstrual cycle, pregnancy, and menopause. These factors may also be operative with respect to the higher incidence of thyroid carcinoma.

Males constituted 25% of the papillary group, 20% of the follicular group, and 12% of the anaplastic group. At onset of goiter, proportionately higher percentages of males were in the first, third, and seventh decades (Table 4). The same was true for males in the papillary group (Table 9) The age at onset of carcinoma also showed a proportionately higher percentage of males in the first, third, and seventh decades (Table 5), and this increased percentage was made up of those with papillary carcinoma (Table 10). Table 6 (age at operation) also shows the first, third, and seventh decades to have the higher percentages of males, and these were again in the papillary group (Table 11) The

Table 10



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Chapter IV

ORIGIN AND ETIOLOGY OF THYROID CARCINOMA

Relation to Nodular Goiter

EVIDENCE that the majority of the thyroid carcinomas arose in pre-existing, benign nodules or adenomas was suggested by the incidences (7.1 to 25.5% range) of carcinoma in several series of non-toxic goiters and in the relatively long preoperative course of many thyroid carcinomas (11) Other accumulating evidence, however, suggests that most thyroid carcinomas do not originate in this fashion In a histologic comparison of benign and malignant thyroid neoplasms, Meissner and McManus (12) concluded that the latter were, as a rule, malignant from the beginning, and that benign thyroid nodules rarely became malignant secondarily. The same conclusion was reached more recently by Sloan (13) in his careful study of 282 patients with thyroid carcinoma. Sloan noticed a significant discrepancy between the incidence of nodular goiter, both endemic and sporadic, and the incidence of thyroid carcinoma in comparable age groups, and concluded that if carcinoma did develop from benign nodules, the incidence of thyroid cancer should increase during later life. From the histologic studies in the present report, one would suppose that, if thyroid carcinoma developed in pre-existing, benign thyroid nodules, the type of carcinoma probably would be follicular since benign nodules are usually follicular and benign papillary nodules are rare Since the most common type of carcinoma is papillary, however, this suggests that carcinoma probably rarely arises in a previously benign nodule or adenoma

Cole (11) has stated that both nodular goiter and thyroid carcinoma are geographic diseases, and has cited the incidence of each

relatively higher incidence of thyroid carcinoma in males in the first and seventh decades might be accounted for by a relative increase in estrogenic activity at those times, but this possibility does not explain the similar relatively higher incidence in the third decade.

were associated with these benign nodules. Of 25 glands containing anaplastic carcinomas, four (16%) also contained such nodules. The higher observed incidence of benign nodules associated with follicular carcinoma suggests a relationship between these benign and malignant lesions. It seems quite apparent, however, that most thyroid carcinomas probably originate in otherwise normal thyroid glands.

Relation to Toxic Diffuse Goiter

It has been recognized that thyroid carcinoma is rarely found in hyperplastic glands (toxic diffuse goiter) of Graves' disease. In the present study, a diagnosis of hyperthyroidism, based on clinical and laboratory data at the time of operation, was made in six patients. However, only one patient with a small papillary carcinoma displayed a hyperplastic thyroid gland characteristic of Graves' disease. The other five patients, two with papillary carcinoma and three with follicular carcinoma, had either associated benign nodular goiters or otherwise normal appearing thyroid glands. In the past 10 years, we have observed several small thyroid carcinomas (not included in this series) found incidentally in hyperplastic thyroid glands of patients with Graves' disease. These few patients, however, had preoperative therapy with thiouracil.

Relation to Hashimoto Disease

In a previous report from the University of California Hospital, concerned with the relationship of Hashimoto disease and carcinoma of the thyroid gland, it was concluded that both histologic and statistical relationships existed between these two disease processes (22) Table 12 shows the incidence of thyroid carcinoma in thyroid glands with and without associated Hashimoto disease The

Table 12

INCIDENCE OF THYROID CARCINOMA WITH ASSOCIATED HASHIMOTO DISEASE

Incidence in Hashimoto Population		
Total Hashimoto population	335	
Thyroid carcinoma with Hashimoto disease	70	20%
Incidence in Non-Hashimoto Population		
Total non-Hashimoto population	7,423	
Thyroid carcinoma without Hashimoto disease	223	3%

process in endemic and nonendemic areas. Ward (14), in 1935, surveyed the incidence of diffuse and nodular goiter and various types of thyroid carcinoma in four geographic areas. The incidence of nodular goiter was, of course, lower in a nonendemic area, California, than in endemic Switzerland. In California, papillary carcinoma was more common than follicular carcinoma, and in Switzerland, follicular carcinoma occurred far more frequently than papillary carcinoma. Thus both in California and in Switzerland, there was an inverse relationship between the frequency of nodular goiter and papillary carcinoma. In more recent years, papillary carcinoma is still uncommon in all parts of Switzerland, including Zurich, Berne and Geneva (personal communications 15, 16, and 17). Although thyroid carcinoma was found in 7% of autopsies at the Pathologic Institute of the University of Zurich from 1948 to 1952, none was the papillary type (18).

In the present study, it was concluded that papillary carcinoma arises in almost all instances from thyroid glandular parenchyma and not from pre-existing, benign nodules Wegelin (19) has described the origin of thyroid papilloma in macrofollicular colloid nodules. In addition, beginning neoplastic papillary proliferation from the lining of degenerated cystic benign nodules has been observed in our pathologic material, and the possibility does exist that some papillary carcinomas may originate in this fashion.

It seems likely that the localized, circumscribed, follicular carcinomas, classified by some authors as malignant adenoma or angioinvasive adenoma (20, 21), may originate as benign lesions, and that eventually capsular or vascular invasion may occur in them This conclusion is suggested because of the histologic and cytologic similarity between benign and malignant circumscribed nodules of this sort Three and possibly four of the invasive follicular carcinomas in the present study appear to have originated in pre-existing microfollicular or macrofollicular adenomas. In the fourth case, neoplastic tissue was invading both within a benign nodule and in adjacent thyroid parenchyma, and its origin could not be accurately determined

Of the 180 thyroid glands with papillary carcinoma, 31 (17%) contained benign microfollicular or macrofollicular nodules or adenomas. Twenty-five (28%) of the 88 follicular carcinomas

been studied by Mustacci (30). Underwood and co-workers (31) noted a close association of pregnancy with the appearance or progression of papillary carcinoma in 9.8% of their female patients. In the present study, 12 female patients (13%) had papillary carcinoma demonstrable first during or immediately following pregnancy; these patients ranged from 20 to 41 years of age, with a mean age of 28. There were 78 other females (86%) with papillary carcinoma originating between 16 and 45 years of age whose clinical records indicated no relationship between pregnancy and onset of the thyroid carcinoma. Fourteen of these 78 patients were single.

Of two female patients with follicular carcinoma, age 23 and 24, respectively, one had developed thyroid neoplasm during her first pregnancy. In the second patient, the malignant thyroid nodule was discovered six months following termination of pregnancy. There were 23 other females with follicular carcinomas in the 16-to 45-year age group, none was single.

Three female patients with anaplastic thyroid carcinoma were in the 16- to 45-year age group. In no instance did the neoplasm originate during pregnancy.

The frequency of pregnancy in young females, the frequency of physiological thyroid enlargement during pregnancy, and the higher incidence of papillary carcinoma in young females make the relationship between pregnancy and thyroid carcinoma of doubtful significance. The complete physical examination usually made during pregnancy undoubtedly revealed thyroid carcinomas which otherwise would only have been discovered later. There was no evidence that thyroid carcinomas observed in pregnant females were unusually active or advanced (31).

Relation to Irradiation

The studies of Duffy and Fitzgerald (32) have stimulated considerable interest in the possible effect of irradiation of the thyroid gland during childhood on the subsequent development of thyroid carcinoma Other studies have confirmed the high incidence of thyroid carcinoma in children who had received previous irradiation to the cervical or thymic areas (33, 34). Uhlman (35), however, does not accept the correlation between previous radiation therapy and the development of thyroid carcinoma. Until a control of pa-

difference in the incidence of thyroid carcinoma in the two groups is highly significant statistically ($X^2 = 282.15$ with 1 df). The present study confirms both the apparent histologic and statistical relationships between these two processes. Distinct transitions between the proliferating epithelium of Hashimoto disease, described originally by Williamson and Pearse (23), and frank infiltrating thyroid carcinoma are demonstrable in some instances, and some portions of the proliferating epithelium midway between the two extremes cannot be classified either as benign or malignant with certainty. Fifty-three (29%) of 180 glands containing papillary carcinoma also showed Hashimoto disease, as did four (16%) of 25 glands containing anaplastic carcinoma. Thirteen of 88 (14%) with follicular carcinoma also showed the Hashimoto process in the thyroid parenchyma. Of the 70 cases of Hashimoto disease in this group of patients with thyroid carcinoma, the Hashimoto lesion was diffuse in 57 and focal in 13. It should be emphasized that these cases included 1) carcinomas found incidentally in glands removed surgically for Hashimoto disease, and 2) Hashimoto disease found incidentally in glands removed for thyroid carcinoma.

A relationship between non-epithelial malignant thyroid neoplasms and Hashimoto disease has also been suggested (6, 24, 25) In the latter report, coexisting sarcoma, adenocarcinoma, and Hashimoto disease were described in a single thyroid gland In the present report, a male patient with papillary carcinoma had a coexisting giant cell sarcoma of the thyroid gland This sarcoma was identical with one reported by Rather (26).

Relation to Miscellaneous Thyroid Disease

Thyroid carcinoma originating in a thyroglossal duct cyst has been reported (27). In the present study, a papillary carcinoma in a female patient was found in the inferior segment of a thyroglossal duct Origin from atypical thyroglossal epithelium was not demonstrable, and this particular carcinoma was no different from the majority of papillary thyroid carcinomas

A single case of thyroid carcinoma associated with subacute thyroiditis has been reported (28). We have observed a similar case, not included either in the present or previous studies (2, 29).

Relation to Pregnancy

A relationship between thyroid carcinoma and pregnancy has

Blood Groups. The expected and observed ABO and Rh blood groups in these patients with papillary, follicular, and anaplastic thyroid carcinoma are shown in Table 13 At the University of California Hospital, the expected percentages of blood groups were: 45% O, 40% A, 11% B, 4% AB, and 85% D.

There were no significant differences between the expected and observed ABO blood groups in patients with papillary (X_2 = 4.2544 with 3 df), follicular (X_2 = 0.9309 with 3 df), or anaplastic (X_2 = 2.086 with 3 df) (P = 0.2 — 0 1). There were no significant differences between the expected and observed D positive and negative blood groups in these patients. Also, there were no significant differences between the expected and observed ABO and Rh blood groups in either males or females, when each sex was studied separately.

Congenital Anomalies. Congenital anomalies or diseases were described in only eight patients with thyroid carcinoma (seven papillary and one anaplastic). These defects included harelip and *cleft palate, congenital cataract, trigger thumb, hammer toe, dis*location of hips, deformities of toes, bilateral Dupuytren's contracture, and progressive muscular atrophy

Table 13

Blood Groups of Patients With Thyroid Carcinoma

	PAPILLARY		FOLLICULAR		ANAPLASTIC	
	Observed	Expected	Observed	Expected	Observed	Expected
O	59	54 0	12	13 05	6	6 30
A	53	48 0	11	11 60	5	5 60
B	6	13 2	4	3 19	3	1 54
AB	2	4 8	2	1 16	0	0 50
D pos	100	100	24	26 4	9	8 5
D neg	18	18	7	4 6	1	1 5

tients for whom similar cervical or thymic irradiation was indicated but not given can be studied, this relationship remains of tremendous interest, but not yet of proved significance.

Development of thyroid neoplasms in rats subjected to various experimental procedures, including internal and external thyroid irradiation, has been described (36 to 46). Since these induced neoplastic lesions, both benign and malignant, are similar or identical in irradiated and non-irradiated rats, it would appear that they represent examples of hormonal carcinogenesis rather than neoplasms resulting from irradiation *per se* (44). Although malignant neoplasms in human thyroid glands following external thyroid radiation are rare (47), development of multiple proliferating thyroid adenomas has been observed (48). Possible further and malignant alteration seems likely in such post-irradiation nodules in the human being. Recently a low-grade carcinoma has been described in a 17-year-old girl, eight years after irradiation with I_{131} for Graves' disease (49)

In the present study, only two patients were known to have received previous thyroid irradiation A 59-year-old female with a follicular carcinoma of the thyroid gland had received external thyroid irradiation 15 years earlier for toxic diffuse goiter The second patient, a male with papillary carcinoma, had had a goiter for 21 years. Five years before entry into the hospital, he had received external thyroid irradiation for hyperthyroidism. Since many of the patients in the present study were observed prior to the observations of Duffy and Fitzgerald (32) and Clark (33), the clinical records of the University of California are probably not reliable in indicating how many of these patients had received previous thyroid irradiation during infancy or childhood During the past two years, two patients have been observed with papillary carcinoma that appeared when the patients were 16 years of age. Both had received cervical irradiation during childhood. They are not included in the present study.

Genetic Relationships

Race. Most of the patients were Caucasians. There were one negro female, three Chinese females, and one Japanese female with papillary carcinoma, and one Japanese female with anaplastic carcinoma.

area. This frequency was essentially the same as that of a control group of patients at the hospital (2).

Table 15

ENDEMIC RESIDENCE OF 293 PATIENTS WITH THYROID CARCINOMA

PAPILLARY		
Male	15	(33%)
Female	66	(48%)
FOLLICULAR		
Male	12	(66%)
Female	35	(50%)
ANAPLASTIC		
Male	2	(66%)
Female	14	(63%)

Symptoms

Of the 293 patients, 286 had goiter, in most instances noted by the patient at the age indicated in Tables 4 and 9. No history of goiter was obtained in seven patients. In the papillary group, 28 goiters, usually single nodules, had not been noted by the patient but were discovered by a physician during routine physical examination. Eleven follicular carcinomas were also discovered accidentally or on routine examination, but all anaplastic carcinomas were evident first to the patients.

Table 16

INITIAL SYMPTOMS OF THYROID CARCINOMA

	PAPILLARY (180)		FOLLICULAR (88)		ANAPLASTIC (25)	
	Male (45)	*Female (135)*	*Male (18)*	*Female (70)*	*Male (3)*	*Female (22)*
Pressure	11	52	7	29	1	15
Recent growth	29	71	8	48	2	20
Hoarseness	6	28	3	19	0	11
Pain or tenderness	3	12	1	4	6	6

The frequency of initial symptoms of cervical pressure (including dysphagia and cough, recent growth, hoarseness, and pain and tenderness) is shown in Table 16 The ages at clinical onset of symptoms of recent growth, pressure, and initial complaint due to local or distant metastases rather than goiter are shown in Table 17. In general, the distribution of ages at clinical onset of symptoms closely follows the distribution of ages at onset of carcinoma.

Chapter V

CLINICAL STUDY OF PATIENTS WITH THYROID CARCINOMA

Family History

TABLE 14 shows the numbers and percentages of patients with the three major types of thyroid carcinoma who had a family history of goiter. These included 70 (23%) of the 293 patients, 25% of the females and 18% of the males. Of the 293, 78 (26%) had a family history of malignant neoplasms, 19% of the males and 24% of the females (Table 14). In a control group of patients at the University of California Hospital, 25% had a family history of malignant neoplasms (2), a value not significantly different from that of the group of patients with thyroid carcinoma.

Table 14

FAMILY HISTORY OF GOITER AND MALIGNANT NEOPLASMS

		Goiter	*Malignant Neoplasms*
PAPILLARY			
	Male	9 (20%)	6 (13%)
	Female	34 (25%)	40 (29%)
FOLLICULAR			
	Male	4 (22%)	5 (27%)
	Female	14 (20%)	21 (30%)
ANAPLASTIC			
	Male	0 (0%)	2 (66%)
	Female	9 (40%)	4 (18%)

Past History

Of the 293 patients, 144 (49%) had lived in endemic areas, either in the United States or elsewhere These constituted 42% of the males and 50% of the females. (See Table 15.) Previous studies at the University of California Hospital have shown that 49% of patients with Hashimoto disease had lived in an endemic

the diagnosis of thyroid carcinoma. According to Searls, the thyroid nodule in a female patient who is beautiful is likely to be carcinoma. However, Searls has recently pointed out that this sign *cannot be used by older physicians since to them all women may* appear beautiful.

Other diseases of endocrine origin were uncommon in these patients with thyroid carcinoma, occurring in only four female patients in the papillary group. These included one with alopecia, one with "endocrine" obesity, one with diabetes mellitus, and two with parathyroid adenomas producing hyperparathyroidism. In the latter two, thyroid carcinomas were discovered during parathyroidectomy.

Of the 293 patients, 12 (4%) had a pre-operative clinical diagnosis of hyperthyroidism Review of the clinical records suggested, however, that only 6 (2%) showed sufficient clinical or laboratory evidence (as judged by basal metabolic rate and levels of protein-bound iodine) to justify a diagnosis of hyperthyroidism. Of these six patients, three had papillary carcinoma and three follicular carcinoma. Of the 293 patients, 14 (4%) showed clinical or laboratory evidence (as judged by basal metabolic rate and levels of protein-bound iodine) of hypothyroidism. Of these 14 patients, 12 *had papillary carcinoma and two had follicular carcinoma.*

Pre-operative Diagnosis

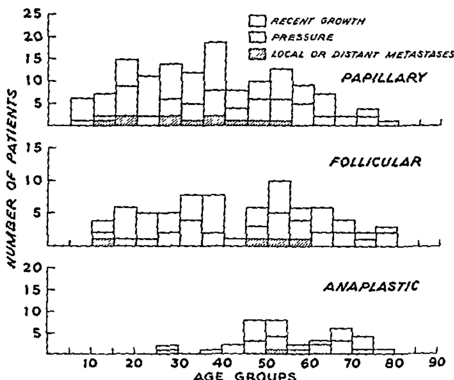
The pre-operative clinical diagnosis made on the 293 patients are summarized as follows:

Carcinoma	118
Multi-nodular goiter	103
Single nodular goiter	35
Colloid goiter	4
Thyroiditis	5
Miscellaneous (including Graves' disease)	17
No diagnosis	11
Total	293

The pre-operative impressions as to whether the thyroid nodules were single or multiple are compared with the post-operative findings in Table 18 These data indicate that clinical examination does not always reveal multiple nodules apparent on pathologic examination.

Table 17

AGE AT CLINICAL ONSET OF SYMPTOMS OF THYROID CARCINOMA



Pressure symptoms with concurrent recent growth have been characteristic of the clinical histories of patients with thyroid carcinoma described in previous reports of studies from this hospital (50, 51). Thirteen patients had initial complaints referable to local regional metastases in lymph nodes and three had complaints referable to distant metastases (skeleton, breast, skin, and pleura)

Physical Signs

The most significant point noted on physical examination of these patients was the presence of a solitary nodule, since it has been shown that 11 to 24% of such nodules are likely to be malignant regardless of other factors (50, 51). The consistency of the nodule does not always aid in the diagnosis, since many malignant neoplasms were soft and many benign nodules were hard due to hemorrhage or calcification. Searls (52), at the University of California Hospital, has described a sign which may be useful in

Table 19

Diagnosis of Thyroid Carcinoma, First Established Clinically, at Operation, or in the Pathology Laboratory			
	Clinical	*Surgical*	*Pathological*
PAPILLARY	66	32	76
FOLLICULAR	29	11	43
ANAPLASTIC	23	2	0

Table 18

PREOPERATIVE AND POSTOPERATIVE DIAGNOSIS OF SINGLE NODULAR OR MULTINODULAR GOITER

		Preoperative	Postoperative*
PAPILLARY (180)			
	Single	123	108
	Multiple	46	70
	None	11	2
FOLLICULAR (88)			
	Single	59	43
	Multiple	25	45
	None	4	
ANAPLASTIC (25)			
	Single	10	11
	Multiple	14	14
	None	1	

* Diagnosis made at operation, in laboratory, or both

Most patients had pre-operative laryngoscopy to determine the status of vocal cords. Twenty-two (7%) had weakness or complete paresis of one vocal cord: papillary, 8 (4%); follicular, 8 (9%), and anaplastic, 6 (24%). Five patients who had initially been operated upon elsewhere had post-operative paresis or paralysis of vocal cords at the time of entry to the University of California Hospital. Few of the clinical records indicate that the remainder of the patients had been given a post-operative examination of the vocal cords Previous studies from this hospital (51) showed that paralysis of a vocal cord was suggestive of malignancy, but that hoarseness alone was not

The correct diagnosis of carcinoma in the 293 patients was established first from the clinical examination, from examination at the time of thyroidectomy, or in the pathology laboratory. These data are summarized in Table 19

thyroid gland were classified as Grade II. As a rule, these were less differentiated and showed greater degrees of cellular pleomorphism and more numerous mitotic figures, particularly in their peripheral portions.

Neoplasms displaying extensive growth in the thyroid gland, often with extra-glandular invasion, were considered as Grade III. Almost without exception, these had anaplastic, de-differentiated patterns, and consisted of cells which were pleomorphic and had rich, nuclear chromatin. Multinucleated cells and mitotic figures were numerous.

Such grading is necessarily somewhat arbitrary since overlapping between Grades I and II and between II and III is occasionally observed. Such grading is an indication of the extent of the neoplasm, since, presumably, earlier or perhaps more slow growing neoplasms would be expected to be relatively localized, whereas lesions of longer duration and those with more rapid growth would be expected to be more extensive within the thyroid gland. The corresponding cytologic patterns are compatible with this concept.

Gross Features of Thyroid Carcinoma

There is an increasing reliance by thyroid surgeons on immediate diagnosis by frozen section at the time of the thyroidectomy. Although the frozen section technique has been used widely for many years in diagnosis at operation for tumors of the breast, its use in conjunction with thyroid surgery is comparatively recent. Establishment of a definitive diagnosis of thyroid carcinoma during the initial operative procedure can be followed by more radical thyroidectomy and by dissection of cervical lymph nodes, if desirable, thus obviating a second operative procedure after a diagnosis of thyroid carcinoma has been made microscopically from permanent sections.

In actual practice, the gross appearances of a thyroid nodule may be more helpful in immediate diagnosis than are the cytologic and histologic patterns observed microscopically in the rapid-frozen section. The gross aspects of the thyroid nodule denoting malignancy must be confirmed by microscopic examination, but even experienced pathologists are only too familiar with the difficulties in preparing and interpreting frozen sections of certain thyroid lesions.

Chapter VI

PATHOLOGIC STUDY OF THYROID CARCINOMA

Classification of Thyroid Carcinoma

At present there is a tendency toward simplification of histologic classification of thyroid carcinoma. The classification proposed by Warren and Meissner (4), separating thyroid carcinomas into papillary, follicular, and anaplastic types, has been generally accepted among pathologists interested in thyroid disease, and offers certain advantages over more elaborate schemes of classification. It should be emphasized strongly, however, that certain difficulties arise in the use of this classification. For example, most carcinomas which are mainly papillary display considerable follicular and lobular differentiation Psammoma bodies which are characteristic of papillary carcinomas occasionally may be found in follicular carcinomas. The metastases from primary follicular carcinomas may display papillary patterns Some portions of either papillary or follicular carcinomas, either in primary sites or in metastases, may have anaplastic, undifferentiated patterns with exceedingly pleomorphic cells. And finally, basically anaplastic thyroid carcinomas may contain small areas displaying papillary, follicular, or lobular patterns. An attempt at resolution of these problems is included in a later section of the present report

Grading of Thyroid Carcinoma

The system of grading employed in this study was described by Warren (5). Malignant thyroid neoplasms which were encapsulated, circumscribed, or only invading the adjacent gland or blood vessels in a minimal fashion were placed in Grade I. As a rule, these neoplasms were well differentiated, had papillary, follicular, or trabecular patterns, and consisted of fairly uniform cells with minimal, if any mitotic activity.

Neoplasms showing more extensive infiltration of the surrounding

A significant number of invasive papillary carcinomas are densely scarred centrally, whereas peripherally they are softer and contain less fibrous tissue. These findings are consistent with the microscopic patterns observed in many of these neoplasms. Some small carcinomas are scarred and appear stellate (sclerosing tumors of the thyroid gland) Calcification is evident in many papillary carcinomas, and areas of cartilaginous or bony consistency in some. Calcific deposits often occur centrally, either extensively or in scattered, small flecks. It should be emphasized that calcification is not proof of a benign thyroid process.

Anaplastic thyroid carcinomas (Group III) have many of the gross features of papillary or follicular carcinomas, although as a rule they are larger, bulky neoplasms, often extending through the thyroid capsule and widely infiltrating adjacent cervical structures and tissues. They are mostly soft grey, pink, or yellow. The cut surface is rounded or bulging, and frequently displays degeneration, necrosis and hemorrhage.

Histologic Features of Thyroid Carcinoma

Papillary Carcinoma. Well-differentiated papillary carcinomas without less-differentiated follicular and lobular structures were composed of large, uniform cells lying on delicate, vascular, connective tissue stalks (Fig. 1) These papillary structures were often folded in a complicated, irregular fashion The cells were large, the majority averaging 22 to 36 microns in diameter, but ranging from 20 to 50 microns The nuclei were correspondingly large, averaging 14 microns in diameter These nuclei were characterized by delicate nuclear membranes and sparse, delicate, intranuclear chromatin. Large segments were devoid of chromatin, so that these nuclei characteristically appeared opaque and as though composed of ground glass As a rule, nucleoli were small, if present, although in some neoplasms they were large, discrete, and pale eosinophilic. Mitoses were few Phase microscopy revealed more abundant, coarse nuclear chromatin and more numerous large, irregularly outlined nucleoli. Folding and indentation of nuclear membranes were frequent and were only observed regularly with phase microscopy

The cytoplasm of these cells was abundant, finely granular, and often extensively vacuolated The vacuoles caused nuclear com-

The gross appearances of thyroid carcinomas vary with the size, extent, type, and degree of differentiation. Well-differentiated, malignant thyroid neoplasms, either papillary or follicular (Group I) may closely resemble their benign counterparts, papillary or follicular adenomas. Thus the malignant, but early well-differentiated lesions may be distinctly circumscribed or even encapsulated, and present a homogeneous, uniform cut surface. The tissue of differentiated papillary carcinomas may be either finely granular or frankly papillary with visible, finger-like processes or fronds. Such lesions are often cystic, with turbid, lipid-containing or sanguineous fluid. The tissue of differentiated follicular carcinomas, like that of follicular adenoma, as a rule appears homogeneous and glistening, and yellow, pink, or tan in color. Such circumscribed or encapsulated but malignant neoplasms are usually easily distinguished from adenomatous nodules which are obviously well supplied with colloid and display a variegated cut surface resulting from hemorrhage, degenerative changes, fibrosis, and calcification.

More extensive and less well differentiated neoplasms (Group II) can usually be recognized as malignant These nodules may be circumscribed without encapsulation or, if partly encapsulated, may display perforation of the capsule and invasion of adjacent parenchyma. In some instances a secondary capsule may surround this locally invasive portion of the nodule, or satellite neoplastic nodules may be found about a larger, central nodule Extension through the thyroid capsule or rarely, invasion of thyroid veins may be observed, and these are obvious signs of malignancy. A large segment of a lobe or an entire lobe may be involved, or extension into the isthmus may be apparent

Most of these invasive thyroid neoplasms are firm, dense, hard, fibrous, and gritty or stony, and are grey-white. The cut surfaces may be opaque or translucent Other nodules with less desmoplastic reaction may be softer and more friable, and appear grey, pink, or yellow, and meaty Unlike the circumscribed or encapsulated nodules, these invasive lesions usually display a flat or slightly retracted cut surface. A variegated cut surface with necrosis and hemorrhage is more often observed in invasive follicular carcinoma than in papillary carcinoma. Unlike adenomatous nodules with degeneration and hemorrhage, the malignant lesions display little or no colloid on their cut surfaces

epithelial cells. This finding suggests that the original central portion of the neoplasm may be destroyed by slow sclerosis, a concept compatible with apparent long duration of some papillary carcinomas. In only one case, the central portion of a small papillary carcinoma was infarcted, necrotic, and hemorrhagic, and displayed early fibrous organization. This acute necrosing process may precede later, dense central sclerosis observed more commonly. Three of these sclerotic lesions could be classified as "sclerosing tumors" of the thyroid (53, 54), and were found incidentally in long standing, multi-nodular goiters in elderly females

Six papillary carcinomas were completely encapsulated intracystic growths (Fig. 2). Some of these lesions may have originated in previously degenerated, cystic thyroid nodules. This sort of origin may be more common than generally suspected, but in Grade II tumors such encapsulation and circumscription may be obscured by the time the tumor is observed pathologically. In only one instance was a papillary carcinoma found infiltrating a thyroid gland adjacent to a benign, macrofollicular thyroid nodule.



Fig 2 Papillary carcinoma. The neoplasm is limited by a thick capsule Note microfollicles at periphery X 120 Hematoxylin and eosin

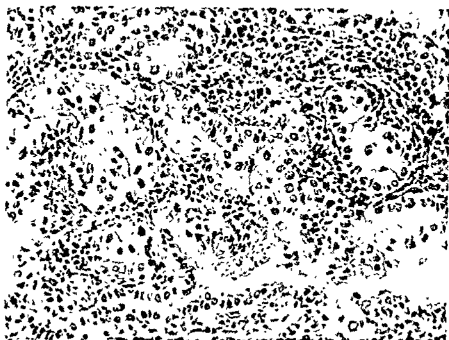


Fig. 1. Papillary carcinoma. No follicular or lobular structures are present. The thyroid epithelial cells have abundant, homogeneous, eosinophilic cytoplasm Lymphocytes and plasma cells infiltrate the stroma X 675 Hematoxylin and eosin.

pression and distortion. In two purely papillary neoplasms the cells were unusually large, and possessed abundant eosinophilic cytoplasm (Hürthle or Askanazy cells). The connective tissue stroma of these neoplasms was heavily infiltrated with lymphocytes and plasma cells. pathologic changes reminiscent of those of Hashimoto disease Of the papillary neoplasms, 25% had a pure papillary pattern, whereas 75% showed admixtures of follicular and solid, lobular structures.

The more common variety of papillary malignant neoplasms as a rule displayed papillary patterns localized mainly in their central portions. Presumably, this was the site of origin of the neoplasm, and such central papillary neoplastic tissue might easily be missed if only a few sections of the tumor were examined histologically. Centrally, nine of the neoplasms showed dense, hyaline fibrous scars, usually containing small or large, calcific deposits. In a few instances, the central portions were devoid of malignant

were usually smaller than those comprising the differentiated papillary portions. Peripherally, the cells averaged 18 to 22 microns in diameter. The nuclei were also slightly smaller than those of the central papillary segments, and averaged 12 to 14 microns in diameter. The nuclear and cytoplasmic characteristics, however, were similar. Usually mitoses were found in small numbers only in the peripheral portions of the papillary neoplasms. In several less well-differentiated papillary carcinomas, some cells in lobular or trabecular groups had abundant eosinophilic cytoplasm (Hurthle or Askanazy cells). Some less-differentiated papillary carcinomas consisted mainly of cells with clear, vacuolated cytoplasm, but the nuclear characteristics of these neoplasms were not different from those of other papillary neoplasms. Although follicular differentiation was common in papillary carcinoma, the cytologic and histologic patterns of these follicles showed distinct differences

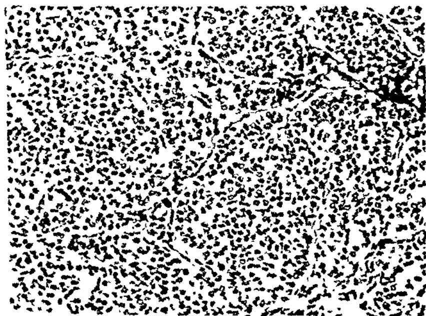


Fig 4 Papillary carcinoma The central portions of this neoplasm were papillary and follicular. The periphery shown here has a lobular pattern although a few microfollicles are present These cells resemble those of the papillary and follicular portions. X 240 Hematoxylin and eosin

In two male patients aged 20 and 25, respectively, enlarged cervical lymph nodes infiltrated by papillary carcinoma were the presenting complaints. Neither patient had a palpable thyroid nodule, and neither has been subjected to thyroidectomy. The histories of these two patients have been followed for 15 and 19 years, respectively, and both men are apparently well, without evidences of malignant disease. It seems likely that both have small, non-palpable, primary, papillary, thyroid carcinomas, a concept previously reported from this and other hospitals (55 to 58).

In most papillary carcinomas, the tissue immediately peripheral to the central papillary portion frequently displayed a distinct follicular structure (Fig. 3). These follicles were, as a rule, smaller than normal thyroid follicles, and often did not contain colloid. Even farther from the central portion, and usually found at the infiltrating margin of papillary carcinomas, the cells were arranged in oval or round, solid lobular structures without follicular differentiation. The cells comprising these follicular and lobular portions



Fig 3 Papillary carcinoma The central portion of the neoplasm shown above retains a papillary pattern, whereas the peripheral part shown below is follicular. X 120 Hematoxylin and eosin

Psammoma bodies were characteristic of papillary carcinomas and, in our studies, have not been observed in benign thyroid lesions. Underwood, Ackerman, and Eckbert (31) regard psammoma bodies as an indication of malignancy. These structures were rounded, basophilic, calcific masses having concentric layers, and were found scattered in the neoplastic tissue. They are probably formed in the connective tissue supporting the neoplastic epithelium, but often this relationship is obscure. Identical psammoma bodies are found in meningeal fibroblastomas where they originate in collagen or vascular walls. They were seen more often in better differentiated, papillary carcinomas, but were also found in the peripheral, neoplastic tissue with follicular or even lobular patterns. When found in follicular carcinoma not having papillary structures, their presence probably indicates the basically papillary nature of the particular neoplasm. Other data to be discussed reinforce this concept.

Of the 180 papillary carcinomas, 48 (26%) contained psammoma bodies in the primary neoplasm in the thyroid gland. The age at onset and at operation, of patients with papillary carcinoma with and without psammoma bodies, is shown in Table 20. The duration of the disease from onset to operation in these same patients is shown in Table 21. No significant differences were observed in the age distribution or in the duration of the disease in patients with papillary carcinoma, with and without psammoma bodies. There were no significant differences in the incidence of psammoma bodies in papillary carcinoma occurring in the two sexes ($X_2 = 0.15$ with 1 df) (Table 22).

The well-differentiated papillary carcinomas consisting of large, eosinophilic cells displayed abundant lymphocytes and plasma cells infiltrating the connective tissue stroma of the papillary fronds. In all other papillary carcinomas, including those with peripheral follicular and lobular patterns, infiltrating plasma cells were either very sparse or completely absent

Papillary carcinomas characteristically invaded intraglandular, lymphatic channels This phenomenon was more often observed at the infiltrating periphery of the neoplasm Centrally, lymphatics distended with neoplastic cells were rarely observed, and were probably obscured by the surrounding neoplastic tissue.

from those of true follicular carcinomas. This point will be considered in the discussion of follicular carcinoma.

The peripheral cellular groups in most papillary carcinomas had a lobular pattern and were undifferentiated in so far as follicular and papillary structures were concerned (Fig. 4). This less-differentiated pattern, while representing de-differentiation, is not regarded as pronounced anaplasia, and is compatible with slow growth of the neoplasm and long survival of the patient. On the other hand, anaplastic changes with bizarre, hyperchromatic and pleomorphic cells characteristic of the majority of anaplastic carcinomas may be superimposed on the papillary structure. In nine patients (5%), anaplastic areas were interspersed with the papillary and follicular structures in the primary neoplasm (Fig. 5). These areas characteristically consisted of large, bizarre, hyperchromatic cells, often multinucleated, associated with pronounced mitotic activity. Of these nine patients, seven have died of thyroid carcinoma.



Fig 5. Papillary carcinoma. The papillary pattern is visible on the right The remainder is anaplastic, and consists of bizarre, multi-nucleated, epithelial cells Note the inflammatory reaction. X 120 Hematoxylin and eosin

Table 22

INCIDENCE IN MALES AND FEMALES OF PSAMMOMA BODIES IN PAPILLARY CARCINOMA

	Male	*Female*	*Total*	
PAPILLARY	11	37	M	45
			F	135
				180

Intraglandular, lymphatic extension to the opposite lobe also occurred In two patients the lobe opposite the one containing the primary neoplasm contained scattered psammoma bodies lying in interstitial connective tissue without demonstrable neoplastic cells. This finding suggested that the opposite lobe had been invaded by neoplastic epithelium, presumably through lymphatic channels, followed by death and disappearance of the malignant cells, leaving psammoma bodies behind In three female patients with papillary carcinoma, a discrete primary thyroid tumor had not been demonstrable, but both lobes showed widespread lymphatic permeation by poorly differentiated papillary epithelium containing many psammoma bodies It is of interest that these three glands also showed diffuse Hashimoto disease In only one of these three cases had metastases in cervical lymph nodes occurred. One of these patients, 28 years after operation, is alive and well, without demonstrable malignant disease In these three instances, it is probable that, early in its development, the malignant neoplasm invaded lymphatic channels so that the growth became diffuse rather than temporarily localized as a *nodule*.

Extensive involvement of both lobes by papillary carcinoma has of course suggested a multicentric origin of this kind of malignancy One patient in this study had two discrete papillary neoplasms in one lobe, another patient had a discrete papillary carcinoma in each lobe All these nodules were well circumscribed, and surrounded by hyaline, fibrous capsules The neoplasms in these two patients may have been of multicentric origin Probably in most instances, however, multicentric foci in one or both lobes result from intraglandular lymphatic dissemination

Follicular Carcinoma. For the purposes of this report, the generally accepted classification of Warren and Meissner (4) which

Table 20

PAPILLARY CARCINOMA WITH AND WITHOUT PSAMMOMA BODIES

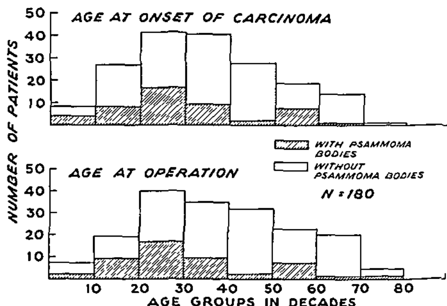
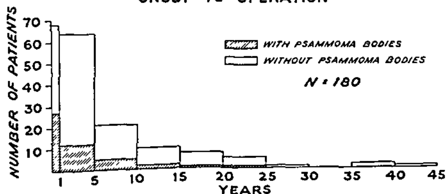


Table 21

DURATION OF PAPILLARY CARCINOMA WITH AND WITHOUT PSAMMOMA BODIES ONSET TO OPERATION



papillary carcinoma already described, including cytologic patterns, psammoma bodies, a few tiny papillary structures in the primary neoplasm, or a papillary pattern in the cervical metastases, were sub-classified as follicular variant of papillary carcinoma. There were 31 of these cases, six males and 25 females. The second distinct group was Grade I, circumscribed or encapsulated thyroid nodules, showing minimal capsular or vascular invasion without extension to the opposite lobe. These were sub-classified as localized follicular carcinoma or invasive adenoma (20, 21). This group consisted of 32 patients, seven males and 25 females. The third group (five males and 20 females) was sub-classified as follicular carcinoma of the widely invasive type. There were no significant differences in incidence in males and females of each subgroup of follicular carcinoma. (Follicular variant of papillary carcinoma, $X_2 = .035$; localized follicular carcinoma, $X_2 = 062$; and invasive follicular carcinoma, $X_2 = .004$ with 1 df.)

Cytology and Histology of Three Subgroups of Follicular Carcinoma

1. Follicular Variant of Papillary Carcinoma. These neoplasms rather closely resembled the more common forms of papillary carcinoma, except that papillary structures were completely absent as a rule In several instances, a few small, poorly defined paoillary structures were found. The predominant patterns were follicular and lobular (Fig. 6) The peripheral portions were usually lobular, a finding identical with that observed in mixed papillary carcinomas The cells had the same range in size and the same opaque, ground-glass nuclei as those described in the papillary group of thyroid neoplasm. The cytoplasm was abundant, and occasionally showed eosinophilic Hurthle or Askanazy characteristics.

2. Localized Follicular Carcinoma (Invasive Adenoma). The pattern of these neoplasms was microfollicular or trabecular (Fig 7) The microfollicles contained little colloid The stroma was sparse and delicate The cells comprising these tumors were significantly smaller than those observed in the follicular variant of papillary carcinoma, and ranged from 10 to 15 microns in diameter Their nuclei ranged from 8 to 11 microns in diameter, and some were as small as 5 microns The nuclei differed signifi-

groups carcinomas according to the predominant pattern was used. The neoplasms presenting a predominantly follicular pattern were classified as follicular carcinoma. In the initial pathologic review, a number of difficulties in the concise use of this definition and classification arose. In some follicular neoplasms, a few very small, poorly defined, papillary structures were observed, and psammoma bodies were occasionally noted. Central scarring and calcification similar to that observed in a number of papillary tumors were also found It seemed apparent that cytologic patterns varied considerably among neoplasms of this group that were initially classified as follicular carcinoma. In the initial clinical review, it was noted that the age incidence at the onset of both papillary and follicular carcinomas showed bimodal distribution, suggesting that each group might consist of heterogeneous populations. The same bimodal characteristics in the age incidence of both papillary and follicular carcinoma were observed by Alhadeff and co-workers (59), and several follicular carcinomas illustrated by these authors had a follicular pattern closely resembling follicular variants of papillary carcinoma. Some follicular carcinomas illustrated by Warren and Meissner (4) had the same characteristics.

Not willing to initiate an entirely new classification of thyroid carcinoma at this time, but recognizing the inherent problems in such classification, we again reviewed the 88 follicular carcinomas in this study pathologically, and classified them as shown in Table 23. Neoplasms having the features of the follicular variant of

Table 23

INCIDENCE IN MALES AND FEMALES OF THREE TYPES OF FOLLICULAR CARCINOMA

	Male	*Female*	*Total*
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA	6	25	31
LOCALIZED FOLLICULAR CARCINOMA	7	25	32
INVASIVE FOLLICULAR CARCINOMA	5	20	25
			88

cantly from those of papillary carcinoma or its follicular variant. They were oval or round, and contained abundant, coarse, chromatin particles, tending to be clustered near the heavy, distinct, nuclear membranes The nucleoplasm between the chromatin particles was deeply basophilic. In most instances, the cytoplasm was relatively sparse. Varying numbers of mitotic figures were present. In two of these nodules having trabecular patterns, the cytoplasm of the neoplastic cells was more abundant and eosinophilic. Such nodules have been classified by others as Hurthle cell carcinoma (60, 61). This cellular characteristic is probably of no prognostic significance Although circumscribed and at least partially encapsulated, vascular invasion was a prominent feature of this group of neoplasms and occurred in nine of the 32 cases.

3. Follicular Carcinoma (Invasive Follicular Carcinoma). Cytologically, these neoplasms resembled localized follicular carcinoma (invasive adenomas) more closely than they resembled the follicular variant of papillary carcinoma. The cells of the neoplasm in this group were characteristically smaller than those of papillary carcinoma, and in the range of, or slightly smaller than, those of localized follicular carcinoma (Fig. 8) The nuclear chromatin was even more plentiful than that of the localized follicular carcinomas, and mitotic figures were generally more numerous Follicles formed by neoplastic cells were numerous (Fig. 9) and contained colloid in many of these neoplasms Phase microscopy did not reveal nuclear structures not visible with routine microscopy The cytoplasm was sparse as a rule. In the neoplasms in this group, three contained groups of Hurthle or Askanazy cells with an abundance of eosinophilic cytoplasm. One follicular carcinoma in this group consisted entirely of these cells, and its pattern was more

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Fig 6 (Top pg 44) *Follicular carcinoma* This neoplasm had no papillary structures However, the cells resemble those of papillary carcinomas, and the nuclei are characteristically pale and opaque. This neoplasm should be regarded as a follicular variant of papillary carcinoma X 675 Hematoxylin and eosin

Fig 7 (Bottom pg 44) *Follicular carcinoma* This neoplasm was localized and encapsulated, but showed minimal capsular and vascular invasion The pattern is microfollicular and trabecular The cells are smaller than those of the follicular variant of papillary carcinoma (Fig 6) and the nuclei are compact and hyperchromatic X 240 Hematoxylin and eosin

Figure 6

Figure 7

trabecular than follicular. Vascular invasion was even more prominent than in the localized follicular carcinomas. A follicular carcinoma arising in a pre-existing macrofollicular adenoma is shown in Figure 10.

Eight (32%) of the neoplasms in this group were extremely anaplastic, had a lobular pattern, and consisted of large, irregular sheets of hyperchromatic neoplastic cells (Fig. 11), frequently



Fig 10 Follicular carcinoma The pre-existing benign macrofollicular adenoma is seen above Below is a follicular carcinoma with a microfollicular pattern *arising in the benign nodule This lesion metastasized to the* left femur X 120 Hematoxylin and eosin

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Fig 8 (Top pg 46) Follicular carcinoma This lesion was invasive, and the pattern is microfollicular and resembles that in Figure 7 The cells, however, are more pleomorphic, and the nuclei are dense and hyperchromatic X 675 *Hematoxylin and eosin*

Fig 9 (Bottom pg 46) *Follicular carcinoma* This invasive lesion has large follicles containing colloid X 675 *Hematoxylin and eosin*

Figure 8

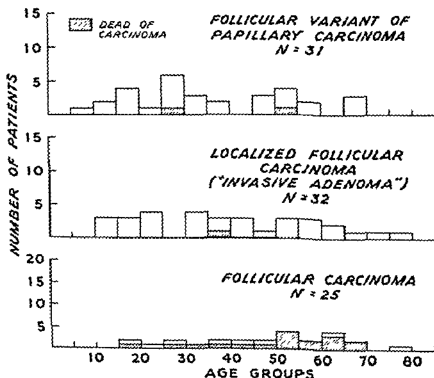
Figure 9

including the frequency of vascular invasion, suggest that the two lesions may represent early and later stages of the same neoplastic process. It also seems likely that, because of the circumscription and encapsulation of localized carcinoma, these lesions may originate as benign adenomas and remain localized and encapsulated until capsular or vascular invasion ensues.

General Features of Follicular Carcinoma

When follicular carcinomas are classified in the three subgroups, differences in the distribution of age at onset and of age at operation in the three groups become apparent In Table 24, showing the age of onset of the three subgroups of follicular carcinoma, ages

Table 24



separated by wide zones of hyaline, connective tissue. In some, few microfollicles remained. Multinucleated cells similar to those seen in the anaplastic areas of papillary carcinoma were not observed. Of these eight patients, six have died of thyroid carcinoma, one is alive and one has been lost to follow-up. All showed extensive vascular invasion. De-differentiation observed in these invasive follicular carcinomas differed considerably from that of most anaplastic carcinomas. In the latter, the majority had, characteristically, extremely bizarre, multinucleated and hyperchromatic cells.

Only the least well-differentiated follicular carcinomas showed accompanying lymphoid infiltration, and this was minimal. None was present in circumscribed Grade I neoplasms.

The cytologic and histologic similarities of localized follicular carcinoma (invasive adenoma) and invasive follicular carcinoma,

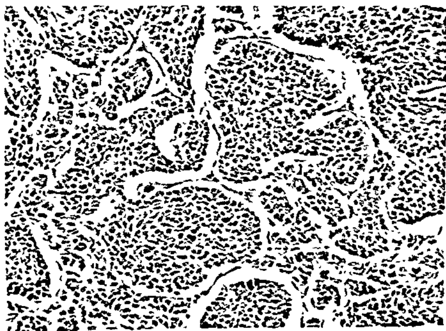


Fig. 11 Follicular carcinoma This lesion is less well-differentiated and has a lobular pattern. The cells and nuclei are similar to those of other better differentiated follicular carcinomas, and are unlike those in the lobular structures in papillary carcinoma (Fig 4). X 240 Hematoxylin and eosin

ly different in the three groups (Table 26). The occurrence of metastases in regional cervical lymph nodes and in distant sites, either at the time of operation or later, differs significantly in the three subgroups of follicular carcinoma (Table 27). The follicular variant of papillary carcinoma (subgroup 1) shows a high inci-

Table 26

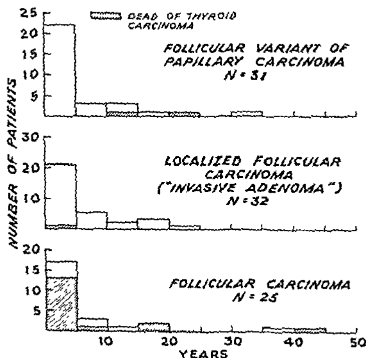


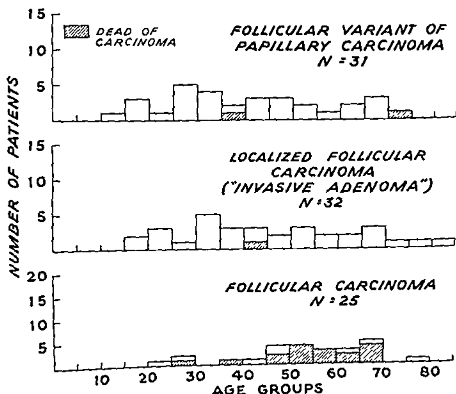
Table 27

METASTASES FROM FOLLICULAR CARCINOMA

		Regional Lymph Nodes	Distant
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA	(31)	14 (45%)	1 (3%)
LOCALIZED FOLLICULAR CARCINOMA ("INVASIVE ADENOMA")	(32)	1 (3%)	3 (9%)
FOLLICULAR CARCINOMA	(25)	3 (12%)	15 (60%)

of patients with the follicular variant of papillary carcinoma show a bimodal distribution similar to that observed in papillary carcinoma (Table 10). Localized follicular carcinoma (invasive adenoma) shows a wide distribution of age at onset, whereas follicular carcinoma (invasive follicular carcinoma) is mainly a disease occurring after the age of 40 years. Similar distributions of ages at the time of operation are shown in Table 25. Of the 20 deaths from follicular carcinoma, only two occurred in patients with follicular variants of papillary carcinoma and one in patients with localized carcinoma. Thus, 17 were the result of invasive follicular carcinoma (Tables 24, 25, and 26). The duration of disease from the onset to the time of operation does not appear to be significant-

Table 25



Many pathologists (62) reserve the term "anaplastic" for those thyroid carcinomas having extremely malignant patterns, with multinucleated giant cells and numerous mitoses.

The predominant anaplastic pattern found in seven of 25 patients in this study was characterized by large sheets and groups of extremely bizarre, neoplastic, epithelial cells. While exceedingly pleomorphic, the majority of these cells was large and often multinucleated (Fig. 12) The nuclei had abundant, coarse chromatin The cytoplasm was, as a rule, abundant and irregularly outlined. Hurthle or Askanazy cells were not observed, however Many cells, both large and small, were elongated and spindle-shaped, producing a pseudosarcomatous pattern. Study of these neoplasms with several connective tissue stains, however, showed no evidence of formation of intercellular reticulum by the neoplastic cells. Mitotic figures, including abnormal ones, were observed frequently. The neoplastic tissue was extremely vascular although extensive necrosis of large segments of the neoplasm was evident.

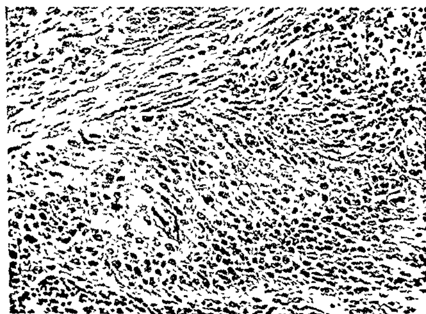


Fig. 13 Anaplastic carcinoma. These neoplasms having an epidermoid pattern are believed to be variants of giant cell, anaplastic carcinomas shown in Figures 5 and 12. X 675 Hematoxylin and eosin.

dence of metastases to regional cervical lymph nodes. This is characteristic of papillary carcinoma. Subgroups 2 and 3 (localized follicular carcinoma and invasive follicular carinoma) show a higher incidence of metastases (both at the time of operation and later) to distant sites, especially in the skeleton, lungs, and brain.

The differences among the three subgroups of follicular carcinoma are both histologic and cytologic. (Differences in survival *will be discussed in a later section of this report.) In addition, the* incidence and character of local and distant metastases clearly indicate that at least two biologically different processes have been included under the general heading of follicular carcinoma as classified by Warren and Meissner (4).

Anaplastic Carcinoma. In the classification of Warren and Meissner (4), the term "anaplastic" is used synonymously with the term "undifferentiated," and in the present study has been applied to those neoplasms having other than papillary or follicular patterns.

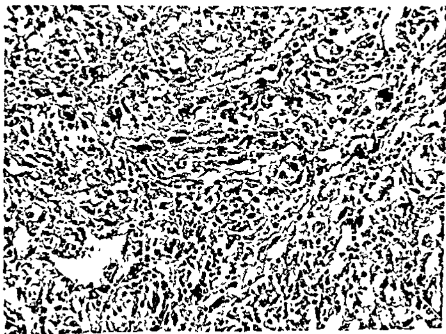


Fig 12 Anaplastic carcinoma. These neoplasms consist of bizarre, pleomorphic cells, many of which are multinucleated Mitoses are numerous. The abundance of spindle cells suggests sarcoma This pattern is identical to that in Figure 5. X 675 Hematoxylin and eosin

terns found in the neoplasm of four patients who survived, following operation, for periods ranging from two to 17 years. The thyroid gland of one patient was also the site of diffuse Hashimoto disease. In addition, the gland was extensively infiltrated by moderate-sized neoplastic cells, in some areas showing such a diffuse infiltrating pattern as to suggest a malignant lymphoma (Fig. 16). The cells were moderately pleomorphic and had oval or round, rather pale, vesicular nuclei, with delicate chromatin networks In some areas, these cells showed a distinct epithelial grouping and had some resemblance to the less well-differentiated portions of papillary neoplasms, but they nowhere displayed a distinct lobular grouping Although this neoplasm contained extremely large numbers of mitotic figures, this patient has survived 14 years following operation. The other three surviving patients had anaplastic neoplasms composed of small or moderate-sized neoplastic cells (Figs. 17 and 18), characterized by compact, extremely hyperchromatic



Fig 15 Anaplastic carcinoma. There is only minimal follicular formation, but the small cells with compact hyperchromatic nuclei are reminiscent of those of follicular carcinoma Note elongated spindle cells. X 240 Hematoxylin and eosin

Three of the neoplasms were epidermoid carcinomas, characterized by moderately well-differentiated, squamous epithelial cells, often having typical intercellular bridges (Fig 13). Formation of keratin and keratin pearls was observed in some groups of cells. One of these epidermoid neoplasms contained interspersed foci of papillary structures and small follicles consisting of cuboidal cells, closely resembling those forming the papillary structures.

The remainder of the anaplastic neoplasms in this group consisted of small or large, oval or round cells, sometimes displaying a lobular or trabecular pattern and, in a few instances, forming microfollicles devoid of colloid (Fig. 14). One neoplasm having this pattern also contained many elongated, spindle-shaped epithelial cells (Fig. 15) along with smaller, round or oval cells. As a rule, mitoses were numerous in these miscellaneous anaplastic neoplasms.

Of considerable interest were the histologic and cytologic pat-



Fig. 14 Anaplastic carcinoma. This neoplasm shows minimal follicular differentiation and is unlike those shown in Figures 5 and 12. The cells and nuclei more closely resemble those of follicular carcinoma X 675 Hematoxylin and eosin.

terns found in the neoplasm of four patients who survived, following operation, for periods ranging from two to 17 years. The thyroid gland of one patient was also the site of diffuse Hashimoto disease. In addition, the gland was extensively infiltrated by moderate-sized neoplastic cells, in some areas showing such a diffuse infiltrating pattern as to suggest a malignant lymphoma (Fig 16). The cells were moderately pleomorphic and had oval or round, rather pale, vesicular nuclei, with delicate chromatin networks In some areas, these cells showed a distinct epithelial grouping and had some resemblance to the less well-differentiated portions of papillary neoplasms, but they nowhere displayed a distinct lobular grouping. Although this neoplasm contained extremely large numbers of mitotic figures, this patient has survived 14 years following operation. The other three surviving patients had anaplastic neoplasms composed of small or moderate-sized neoplastic cells (Figs 17 and 18), characterized by compact, extremely hyperchromatic



Fig 15. Anaplastic carcinoma There is only minimal follicular formation, but the small cells with compact hyperchromatic nuclei are reminiscent of those of follicular carcinoma Note elongated spindle cells X 240 Hematoxylin and eosin

nuclei, and relatively sparse cytoplasm. In two of the neoplasms, mitoses were few, whereas in the third, many were observed.

This histologic study has suggested that anaplastic thyroid carcinomas may have at least two origins. The anaplastic carcinoma characterized by large, bizarre, multinucleated cells seems to represent the anaplastic stage of differentiated papillary carcinoma. The finding of identical anaplastic foci in nine papillary carcinomas, either in the primary neoplasm or in the cervical lymph node metastases, has already been described. Epidermoid carci-

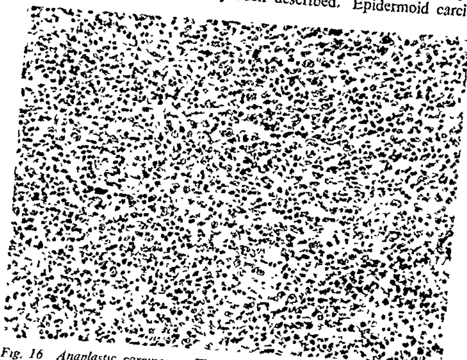


Fig. 16 Anaplastic carcinoma This carcinoma consists of sheets of pleomorphic cells with numerous mitoses Note diffuse chronic inflammatory infiltration This patient has survived 14 years after operation X 240 Hematoxylin and eosin.

Fig 17 (Top pg 57) *Anaplastic carcinoma* The pattern is similar to that shown in Figure 16 but the cells are smaller Diffuse infiltration with lymphocytes and plasma cells is present. X 240 Hematoxylin and eosin

Fig. 18. (Bottom pg 57) *Anaplastic carcinomas* This neoplasm has a small lobular and trabecular pattern The cells are small and have hyperchromatic nuclei resembling those of follicular carcinoma. X 240 Hematoxylin and eosin

Figure 17

Figure 18

noma may be a variant of this line of descent comparable with the occasional observation of adenoacanthoma in the uterus or gastroenteric tract. This idea is suggested by the finding of papillary and follicular structures in one of ther [illegible]

Some of th [illegible] represent the [illegible] carcinoma, since the cellular and nucl[illegible] characteristics (small, compact, hyperchromatic nuclei) are similar to those of better differentiated follicular carcinomas. The finding of typical microfollicles in a few of these anaplastic carcinomas also suggests that the latter have originated from follicular carcinoma.

It is possible, although not proved from this study, that some of the anaplastic, large-cell carcinomas without multinucleated elements may represent still another anaplastic form of papillary carcinoma because of the similarity of their cellular and nuclear characteristics.

The anaplastic carcinomas consisting of bizarre pleomorphic cells and those consisting of more uniform, round cells displayed abundant infiltration with lymphocytes and plasma cells, even in neoplasms which were not necrotic. Few or no chronic inflammatory cells were observed in the spindle-cell anaplastic carcinomas.

It should be emphasized that, in this group of 25 anaplastic carcinomas, an attempt at extensive removal of the gland was not often made because of the extent of the neoplasms. It seems likely that extensive study of more widely representative sections of these lesions should clarify their relationship to better differentiated thyroid carcinomas

General Features of Thyroid Carcinoma

Site of Origin. The sites of origin of carcinoma in the thyroid gland are summarized in Table 28. Wegelin (19) found that the right lobe of the thyroid gland is usually larger than the left and is about one-fifth heavier This degree of difference is approximately the same as the differences in number of papillary and follicular carcinomas arising in the two lobes (Table 28) No sex differences were demonstrable in the site of origin of these thyroid carcinomas.

Weight of Thyroid Tissue Removed at Operation. The tissue removed at surgery, including the primary neoplasm and other

adjacent thyroid tissue, was weighed in the laboratory with the following results:

Papillary carcinoma	Mean weight = 33 gm. (range, 5 — 450 gm)
Follicular carcinoma	Mean weight = 46 gm (range, 5 — 350 gm)
Anaplastic carcinoma	Mean weight = 96 gm (range, 15 — 200 gm)

Table 28

SITE OF ORIGIN IN THYROID GLAND OF CARCINOMA

	Papillary (180)	*Follicular (88)*	*Anaplastic (25)*
Right lobe	91	35	14
Left lobe	77	47	10
Isthmus	7	5	1
Both lobes	1		
Pyramidal lobe		1	
Thyroglossal duct	1		
Lymph node metastases only	2		
Unknown	1		

Table 29

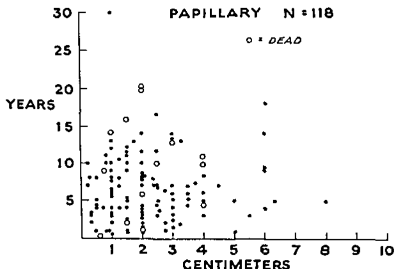


Table 30

DURATION OF THYROID CARCINOMA
RELATION OF SIZE OF CARCINOMA AT
OPERATION TO SURVIVAL AFTER OPERATION

FOLLICULAR N = 43

Table 31

DURATION OF THYROID CARCINOMA
RELATION OF SIZE OF CARCINOMA AT
OPERATION TO SURVIVAL AFTER OPERATION

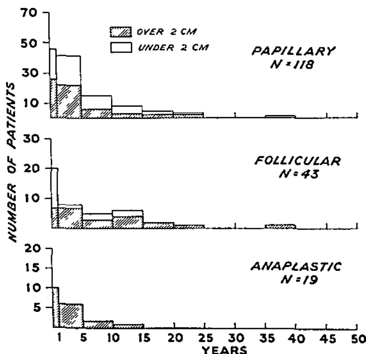
ANAPLASTIC N = 17

These tabulated weights of course included not only that of the neoplastic tissue, but also of the thyroid parenchyma, in some instances containing multiple benign nodules or thyroid tissue affected by Hashimoto disease.

Size of Thyroid Carcinoma. The relation of the maximum diameter of the primary thyroid neoplasm, determined at the time of operation, to survival after operation is shown in Tables 29, 30, and 31. In papillary and follicular carcinoma, no definite relationships appeared to exist between the size of the carcinoma at the time of the first operation and survival following operation. On the other hand, most patients with anaplastic carcinoma survived only for short periods following operation, but had sizable neoplasms, indicating the rapidity of growth of these anaplastic thyroid carcinomas.

Table 32

DURATION OF THYROID CARCINOMA
PRIMARY NEOPLASM OVER OR UNDER 2 CM.



The duration of thyroid carcinoma from onset to operation, in patients with primary neoplasms measuring under or over 2 cm. at the time of operation, is shown in Table 32. No relationship between the duration of papillary or follicular thyroid carcinoma and size of the neoplasm is apparent, suggesting variable rates of growth of these tumors. No anaplastic carcinoma measured less than 2 cm. in diameter.

The lack of significant relationship between the size of primary papillary and follicular thyroid neoplasms and the presence or absence of early and late regional cervical lymph node metastases from these lesions is shown in Table 33 (papillary, $X^2 = 2.3369$; follicular, $X^2 = 0.8761$ with 1 df). Thus there is no apparent relationship between local, intraglandular aggressiveness of these neoplasms and their ability to spread to regional lymph nodes.

Relation of Size to Histologic Grading of Primary Thyroid Carcinoma. The mean diameter of Grade I papillary carcinomas was 1.2 cm., of Grade II papillary carcinomas, 2.5 cm. It would be expected that the larger the neoplasm becomes, the more likely is parenchymal invasion to occur. The extent of the invasion of the gland is one of the criteria used in grading.

The mean diameter of Grade I follicular carcinomas was 2.5 cm., and of Grade II follicular carcinomas, 3.0 cm. These are probably not significant differences. (There were only three Grade III follicular carcinomas.)

The mean diameter of the anaplastic carcinomas was 4.2 cm.; all were Grade III.

Other Thyroid Diseases Associated with Thyroid Carcinoma

The occurrence of other diseases of the thyroid gland already containing thyroid carcinoma is summarized in Table 34.

In this study, adenoma was defined as a benign neoplasm composed of thyroid tissue occurring as a single or multiple nodules (19). No distinction was made between "pure" neoplasms and involutionary or adenomatous nodules.

In a previous study from this hospital, it was shown that a statistical relationship existed between adenoma and Hashimoto disease and between carcinoma and Hashimoto disease. It was also shown that when both adenoma and carcinoma were present in the

Table 33

Relation of Size of Primary Thyroid Carcinoma to Presence or Absence of Regional Lymph Node Metastases	Papillary		Follicular	
	With Metastases	*Without Metastases*	*With Metastases*	*Without Metastases*
Over 2 cm	31	30	4	21
Under 2 cm	21	36	5	13

Table 34

Other Thyroid Diseases Associated With Thyroid Carcinoma	*Papillary (180)*	*Follicular (88)*	*Anaplastic (25)*
Adenoma (total)	31	25	5
Hashimoto disease (total)	54 (focal - 38)	12 (focal - 7)	4 (focal - 1)
Adenoma and Hashimoto disease	13	4	3
Miscellaneous (including colloid goiter, hyperplasia)	4	1	0

Table 35

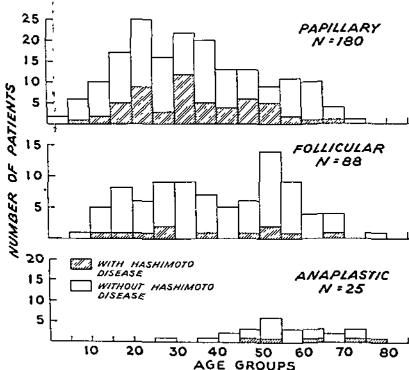


Table 36

AGE AT OPERATION FOR THYROID CARCINOMA WITH OR WITHOUT ASSOCIATED HASHIMOTO DISEASE

PAPILLARY N=180

FOLLICULAR N=88

ANAPLASTIC N=25

WITH HASHIMOTO DISEASE

WITHOUT HASHIMOTO DISEASE

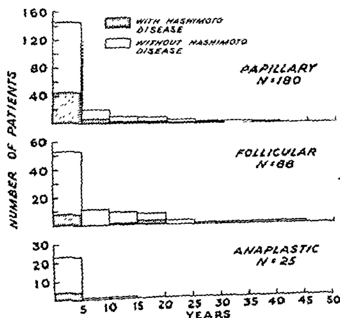
NUMBER OF PATIENTS

AGE GROUPS

10 20 30 40 50 60 70 80

Table 37

DURATION OF THYROID CARCINOMA WITH OR WITHOUT ASSOCIATED HASHIMOTO DISEASE ONSET TO OPERATION



same gland, each was related to Hashimoto disease but not to each other (22). In no way does the pattern of the Hashimoto process differ in thyroid glands with or without thyroid carcinoma. It should also be emphasized that the lymphoid reaction which may result from glandular invasion by thyroid carcinoma differs distinctly from the typical epithelial, lymphoid, and fibrous reaction characteristic of Hashimoto disease (2).

The age at onset, the age at operation, and the duration from onset to operation, of patients with thyroid carcinoma, with or without associated Hashimoto disease, are shown in Tables 35, 36, and 37. Tables 35 and 36 show a higher incidence of Hashimoto disease associated with papillary carcinoma with onset in the 30- to 35-year age group, a period in which the incidence of Hashimoto disease alone is highest (2). There were no other significant differences in distribution of ages at operation or in duration of thyroid carcinoma, with or without associated Hashimoto disease (Tables 36 and 37). The incidence of Hashimoto disease in males and females with each type of thyroid carcinoma is shown in Table 38 There is a significantly higher incidence of Hashimoto disease with papillary carcinoma in females as compared with males ($X^2 = 7.5$ with 1 df) There were no significant differences between the two sexes in incidence of Hashimoto disease occurring with follicular ($X_2 = 0.091$) and anaplastic ($X_2 = 0.649$) thyroid carcinoma.

Table 38

INCIDENCE IN MALES AND FEMALES OF HASHIMOTO DISEASE IN THYROID CARCINOMA

	Male	*Female*	*Total*	
PAPILLARY	6	47	M	45
			F	135
FOLLICULAR	2	11	M	18
			F	70
ANAPLASTIC	0	4	M	3
			F	22
				293

Chapter VII

PATTERNS OF GROWTH OF THYROID CARCINOMA

Invasion of Capsule of Primary Thyroid Neoplasm

OF the group of encapsulated papillary and follicular carcinomas, a diagnosis of early carcinoma, based on microscopic observation of capsular invasion, was made in 19 papillary and in 20 follicular carcinomas

Vascular Invasion

Vascular invasion was observed, either in the gross specimen or, more often, on microscopic examination, in 27 (15%) papillary, 49 (55%) follicular, and 12 (48%) anaplastic carcinomas The determination of vascular invasion did not seem to require the use of specific elastic tissue strains to demonstrate elastic components of vascular walls (4)

Not all thyroid neoplasms displaying vascular invasion metastasized to distant sites Approximately the same percentage of papillary and anaplastic carcinomas showing vascular invasion eventually showed distant metastases, whereas the percentage of follicular carcinomas with distant metastases was less than half the percentage showing vascular invasion in the primary neoplasm. There are probably several reasons for this finding. The neoplasm invading vascular channels may be entirely removed at operation before metastatic spread has occurred Residual neoplastic tissue in the neck after operation may be destroyed by post-operative irradiation. Or neoplastic tissue remaining in the neck or in distant sites may be dependent on the hormonal environment and either may not survive or may remain dormant for long periods without active growth In one of the patients with follicular carcinoma, a vertebral metastasis appeared 12 years after thyroidectomy A second patient had extensive venous invasion in the neck, observed during thyroidectomy, yet died 10 years later of coronary arteriosclerosis, with no evidence of local or distant residual neoplasm.

Lymphatic Invasion

Invasion of lymphatic channels by neoplastic tissue in the lobe of origin at the periphery of the neoplasm was observed in 52 (28%) of the papillary carcinomas but in only 10 (11%) of the follicular and in two (8%) of the anaplastic. Lymphatic invasion in the central part of a thyroid neoplasm may be impossible to demonstrate.

Invasion of Opposite Lobe

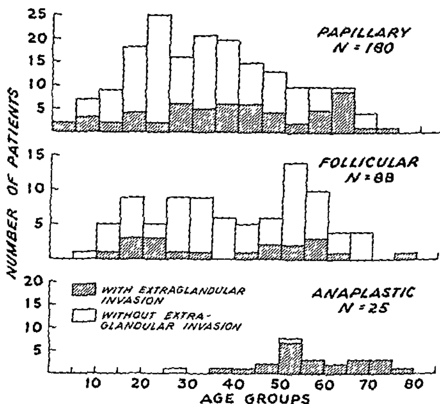
Of the 180 papillary carcinomas, 55 (30%) extended from the lobe of origin to the opposite lobe. This process occurred in 19 (21%) of the 88 follicular carcinomas and in 15 (60%) of the 25 anaplastic carcinomas No localized follicular carcinomas (invasive adenomas) extended to the opposite lobe. Invasive follicular and anaplastic carcinomas appeared to invade the opposite lobe by massive direct extension, whereas papillary carcinomas, as a rule, spread by lymphatic dissemination, to involve the opposite lobe Small, intralymphatic foci of papillary carcinoma were occasionally observed in the opposite lobe, and the finding of psammoma bodies without viable neoplastic tissue in the opposite lobe has been described

Extraglandular Invasion of Thyroid Carcinoma

Extension of the neoplastic process beyond the capsule of the thyroid gland, with infiltration of the trachea, neurovascular bundles, or cervical muscles, was observed at the time of the initial operation in 56 (31%) patients with papillary carcinoma, 19 (21%) with follicular and 23 (92%) with anaplastic carcinoma.

Tables 39 and 40 show the age at onset and age at operation of patients with thyroid carcinoma with and without evidences of extraglandular invasion at the time of the first operation In the papillary group, the incidence of extraglandular invasion appears significantly higher in the older age groups (55 to 65 years). In follicular carcinoma there were no apparent differences in age incidence with or without extraglandular invasion. In the group of anaplastic carcinomas, all but two patients demonstrated extraglandular invasion, a finding compatible with the rapidity of growth and aggressiveness of these neoplasms

Table 39



The duration of thyroid carcinoma from the onset to operation seems to bear no relationship to the presence or absence of extraglandular invasion in the papillary and follicular groups at the time of operation (Table 41) This finding would suggest that the higher incidence of extraglandular invasion of papillary carcinoma in the older age groups is the result of increased aggressiveness of papillary carcinoma at that age, rather than to the length of time the papillary carcinoma was invading the thyroid gland

The incidence of extraglandular invasion in males and females with each type of thyroid carcinoma is shown in Table 42 There were no significant differences between the sexes (papillary, X_2 = 1.01; follicular, 0.06, and anaplastic, 0.34 with 1 df).

Table 40

AGE AT OPERATION FOR THYROID CARCINOMA WITH OR WITHOUT EXTRAGLANDULAR INVASION AT TIME OF FIRST OPERATION

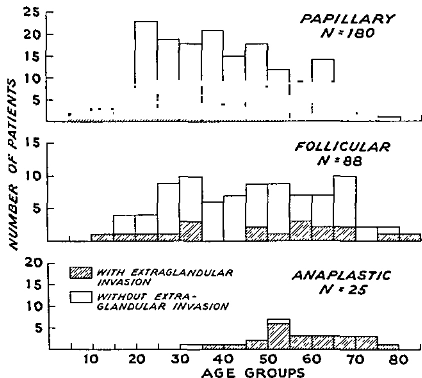


Table 41

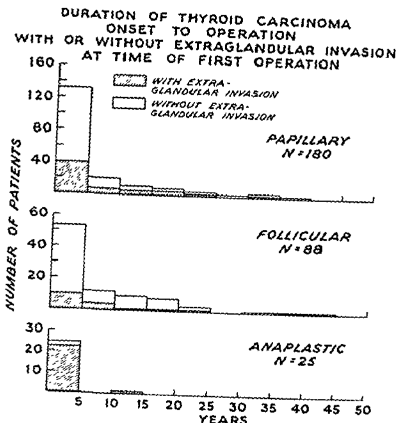


Table 42

INCIDENCE IN MALES AND FEMALES OF EXTRAGLANDULAR INVASION OF THYROID CARCINOMA

	Male	*Female*	*Total*	
PAPILLARY	18	41	M	45
			F	135
FOLLICULAR	5	15	M	18
			F	70
ANAPLASTIC	3	20	M	3
			F	22
				293

Chapter VIII

EARLY METASTASES FROM THYROID CARCINOMA

Regional Lymph Nodes

METASTASES to regional lymph nodes, especially those in the deep cervical chains along the jugular veins, are common in papillary carcinoma. This high incidence of regional lymph node metastases is a reflection of the propensity for lymphatic invasion by papillary carcinoma. Follicular carcinomas metastasize to regional lymph nodes less often, and this finding is consistent with the lesser tendency of these neoplasms to invade lymphatic channels.

Table 43 shows the incidence of metastases in regional lymph nodes in males and females with each type of thyroid carcinoma, initally, at the first operation. There were no significant differences in incidence of regional metastases between the sexes (papillary, $X_2 = 2.80$; follicular, $X_2 = 0.343$; and anaplastic, $X_2 = 1\ 604$ with 1 df).

Table 43

Incidence in Males and Females of Early Regional Lymph Node Metastases in Thyroid Carcinoma

	Male	*Female*	*Total*
PAPILLARY	23	48	M 45 F 135
FOLLICULAR	5	12	M 18 F 70
ANAPLASTIC	0	8	M 3 F 22 293

In 59 (27%) of the 180 patients with papillary carcinoma, regional cervical lymph node metastases were evident clinically, at the time of the first operation or within one or two months after

operation. Of the 121 patients without clinical evidence of regional lymph node involvement, 21 (17%) were found to have histologically positive cervical lymph nodes at the first operation or within one to two months after the first operation. In the latter instances, it was assumed that the metastases in the cervical lymph nodes had been present at the time of thyroidectomy. Thus a total of 80 patients (44%) had papillary carcinoma with early regional lymph node metastases. The sites of these metastases are summarized in Table 44.

Table 44

Regional Lymph Node Metastases at First Operation

	Papillary (180)		*Follicular (88)*	*Anaplastic (25)*
Ipsilateral cervical	62 (34%)		12 (13%)	6 (24%)
Contralateral cervical	20 (11%)		3 (3%)	3 (12%)
(with both thyroid lobes involved)	12 (6%)		2 (2%)	3 (12%)
Bilateral cervical	15 (8%)		4 (4%)	3 (12%)
Midline cervical	8 (4%)	(2 also had lateral metastases)	3 (3%)	0 (0%)
Mediastinal	4 (2%)		0 (0%)	1 (4%)

Of the 20 patients (11%) having contralateral cervical lymph node metastases, 12 (6%) had neoplastic involvement of both thyroid lobes, usually resulting from intraglandular lymphatic dissemination of neoplastic papillary tissue. Of the eight patients (4%) having metastases in midline cervical lymph nodes, two (1%) also had metastases in lateral cervical nodes. These involved nodes in the midline were usually suprasternal, but lay above the thyroid isthmus in one instance.

The locations of both early and late, regional cervical lymph nodes containing metastases from papillary thyroid carcinoma are shown in Table 45. As a rule, the juxtathyroid nodes containing metastatic carcinoma were small, were usually discovered microscopically, and would probably be found more often with careful search. It should be emphasized that papillary carcinoma was found in cervical lymphatic channels near involved cervical nodes in four patients. It is unlikely that such tissue would be removed by

Table 45

Location of Regional Lymph Node Metastases			
	Papillary (180)	*Follicular* (88)	*Anaplastic* (25)
Submaxillary	4 (2%)	1 (1%)	1 (4%)
Upper jugular	17 (9%)	5 (5%)	3 (12%)
Mid-jugular	37 (20%)	8 (9%)	8 (32%)
Low jugular	43 (23%)	8 (9%)	7 (28%)
Spinal accessory	4 (2%)	0 (0%)	0 (0%)
Juxtathyroid	18 (10%)	9 (10%)	7 (4%)
Mediastinal	7 (3%)	0 (0%)	0 (0%)

simple excision of involved, regional cervical lymph nodes. Extranodal, cervical lymphatic involvement was not demonstrated, however, in patients with follicular or anaplastic carcinoma in this study.

Of the 88 patients with follicular carcinoma, 22 (25%) had metastases in regional lymph nodes at the time of the first operation or within one to two months later. In only 11 patients (12%) were regional lymph node metastases evident clinically before operation. Of the 77 patients without clinical evidence of metastases in regional lymph nodes, 11 (14%) had histologically positive, regional cervical lymph nodes at the first operation or within one to two months The sites of these metastases are shown in Table 44. Of the three (3%) patients with contralateral cervical lymph node metastases, two (2%) had neoplastic follicular tissue in both thyroid lobes The locations of both early and late regional metastases in cervical lymph nodes from follicular thyroid carcinoma are shown in Table 45.

Of the 25 patients having anaplastic carcinoma, regional lymph node metastases were evident clinically in 12 (48%) at the time of the first operation or within one to two months. Of the remaining 13 without clinical evidence of metastatic involvement of cervical lymph nodes, only one (7%) had histologically positive lymph nodes at the first operation. Thus a total of 13 (52%) patients with anaplastic carcinoma had early lymph node metastases. The sites of these metastases are shown in Table 44. Of the three (12%) patients with contralateral cervical lymph node metastases, all had anaplastic neoplastic tissue in both thyroid lobes. The lo-

cations of both early and late regional cervical lymph node metastases from anaplastic thyroid carcinoma are shown in Table 45.

The data in Table 45 indicate that metastases in regional cervical lymph nodes from the three types of thyroid carcinomas were more commonly found in those nodes which are closer to the thyroid gland (juxtathyroid and jugular) Frazell and Foote (63) found a similar distribution of involved cervical lymph nodes, and furthermore discovered that, when involvement of lymph nodes was not clinically evident, cervical nodes farther from the thyroid gland were rarely involved, whereas when nodal involvement was clinically evident, the more distant cervical lymph nodes were positive in a significantly higher percentage.

As a rule, the histologic and cytologic patterns of the metastatic carcinoma in cervical lymph nodes closely resembled those of the primary neoplasm Thus, like the primary neoplasm, the metastases may contain well-developed papillary or follicular structures or may be anaplastic In some instances, however, the metastatic carcinoma in lymph nodes showed greater or lesser degrees of differentiation (Table 46) as compared with the primary neoplasm.

Table 46

DIFFERENTIATION OF NEOPLASTIC TISSUE IN PRIMARY THYROID CARCINOMA AND IN CERVICAL LYMPH NODE METASTASES

	Same	*More differentiated in lymph nodes*	*Less differentiated in lymph nodes*
PAPILLARY (180	53	10	7
FOLLICULAR (88)	8	7	1
ANAPLASTIC (25)	10	0	0

It should be noted that the seven cases of follicular carcinoma showing greater degrees of differentiation in the lymph node metastases appear to represent follicular variants of papillary carcinoma Although the pattern of the primary lesion was entirely follicular, without evidences of papillary formation, thus corresponding to the criteria for follicular carcinoma designated by Warren and Meissner (4), in all seven instances the lymph node metastases had distinct papillary patterns, or contained psammoma bodies, or both. In the group of papillary carcinomas, the metastases showing

greater degrees of differentiation than the primary tumor had papillary or even grossly cystic structures. Those less differentiated had macrofollicular or microfollicular patterns, and some were distinctly anaplastic. These variable metastatic patterns occurred with either well-differentiated or poorly differentiated primary papillary carcinomas. Metastases in cervical lymph nodes from anaplastic carcinomas had patterns *identical with those of the* primary neoplasm.

The distribution of ages at onset of thyroid carcinoma and at operation, in patients with or without regional lymph node metastases at the time of first operation, is shown in Tables 47 and 48. In papillary carcinoma, the incidence of lymph node metastases in

Table 47

AGE AT ONSET OF THYROID CARCINOMA WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES AT FIRST OPERATION

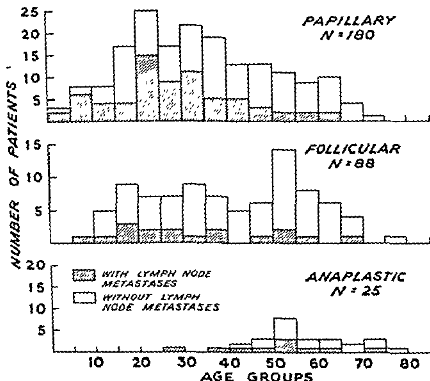
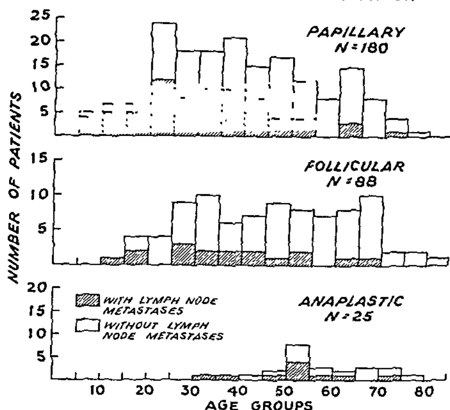


Table 48

AGE AT OPERATION FOR THYROID CARCINOMA WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES AT FIRST OPERATION



the younger age groups is distinctly higher than in the older Significant differences in age incidence of patients with and without lymph node metastases from follicular and anaplastic carcinoma do not exist There appear to be no significant differences in the duration of each type of thyroid carcinoma from onset to operation in patients with and without lymph node metastases (Table 49).

Distant Metastases at Time of First Operation

In the papillary group, only five patients had evidences of distant metastases at the time of the first operation. Two patients had pulmonary metastases, one a metastasis in a clavicle, one a metastasis in a breast, and one a metastatic lesion in the hypopharynx.

In the follicular group, six patients had distant metastatic lesions at the time of the first operation, three pulmonary and three skeletal.

Table 49

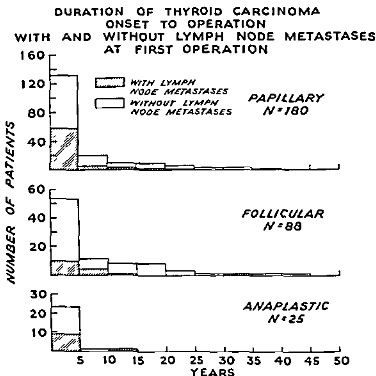


Table 50

INCIDENCE IN MALES AND FEMALES OF EARLY AND LATE DISTANT METASTASES IN THYROID CARCINOMA

	Male	*Female*	*Total*	
PAPILLARY	10	9	M	45
			F	135
FOLLICULAR	2	16	M	18
			F	70
ANAPLASTIC	2	12	M	3
			F	22
				293

In the anaplastic group, none of the patients had evidences of distant metastases at the time of the first thyroidectomy.

The incidence of early and late distant metastases in males and females with each type of thyroid carcinoma is shown in Table 50. Significantly more males with papillary and anaplastic carcinoma had distant metastases than did females (papillary, $X_2 = 7.0$; anaplastic, $X_2 = 4.98$ with 1 df). There were no significant differences in incidence of distant metastases from follicular carcinoma in males and females ($X_2 = 1.214$).

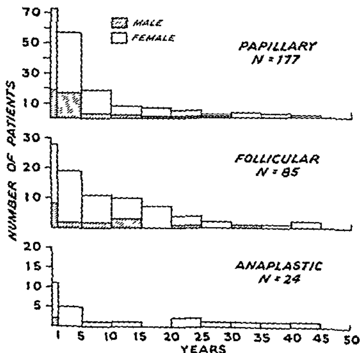
Chapter IX

COURSE OF THYROID CARCINOMA

Of the 293 patients in this study, six with papillary carcinoma and five with follicular carcinoma have been lost to follow-up. Eleven patients with papillary carcinoma and six with follicular carcinoma have died of other causes. Of the patients currently being followed, eight with papillary carcinoma, four with follicular carcinoma, and three with anaplastic carcinoma are alive with known evidences of residual thyroid neoplastic disease, either local or metastatic.

Table 51

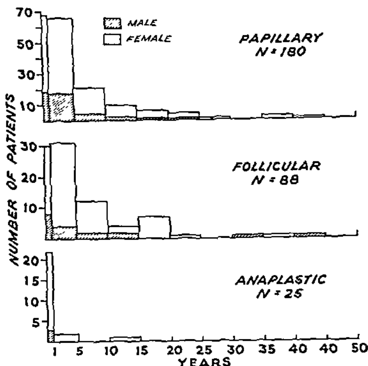
DURATION OF GOITER ONSET TO OPERATION



In the anaplastic group, none of the patients had evidences of distant metastases at the time of the first thyroidectomy.

The incidence of early and late distant metastases in males and females with each type of thyroid carcinoma is shown in Table 50. Significantly more males with papillary and anaplastic carcinoma had distant metastases than did females (papillary, $X_2 = 7.0$; anaplastic, $X_2 = 4.98$ with 1 df). There were no significant differences in incidence of distant metastases from follicular carcinoma in males and females ($X_2 = 1.214$).

Table 52



interval between operation and recurrence was 7.7 years. Of these 22 patients, 11 (50%) have died of papillary thyroid carcinoma.

In the follicular group, 18 patients (20%) have had recurrence in the thyroid region 10 months to 15 years following the first operation. The average interval from operation to the time of recurrence was 4.5 years. Of these 18 patients, 10 (55%) have died of follicular thyroid carcinoma.

In the anaplastic group, 10 patients (40%) had local recurrence in or around the thyroid glandular area. These recurrences were noted after periods ranging from five weeks to 10 years following the initial operation. The average interval between operation and recurrence was 1.7 years. Of the 10 patients with local recurrence, eight (80%) have died of anaplastic thyroid carcinoma.

Four female patients with papillary carcinoma have had recur-

The duration of goiter in patients with the three types of thyroid carcinoma, calculated from the time of onset of goiter to the time of operation, is shown in Table 51. All three types of thyroid carcinoma may be associated with long-standing goiter, for periods of as long as 45 years. In the papillary group, these goiters are probably malignant from their onset, with few exceptions. Benign nodules and Hashimoto disease have accounted for long-standing goiter in some instances in these patients. In the follicular group, probably the majority of goiters originated as malignant neoplasms. In a large number, however, the goiter presumably resulted from the presence of benign nodules or, in some instances, Hashimoto disease. It is of interest that approximately one-third of patients with anaplastic carcinoma had goiters for between five and 45 years prior to operation. Evidences of other thyroid disease were not often found, probably because of the limited extent of examination of representative tissues removed at operation Evidence has been presented to indicate that some of these anaplastic carcinomas may have been preceded by more differentiated, slow-growing thyroid carcinomas producing goiter. This concept is presented in Table 52, where the duration of the majority of anaplastic thyroid carcinomas from onset to operation is shown to have been one year or less. The duration of papillary and follicular carcinoma was similar to the duration of goiter in patients with these two types of thyroid carcinoma.

Table 53 shows the duration of the three types of thyroid carcinoma from onset to operation, in patients under and over 40 years of age. There are no significant differences in duration between the two groups.

Local Recurrence of Carcinoma in Thyroid Gland

Thyroid carcinoma may recur in the thyroid gland following various types of thyroidectomy (64) In addition, recurrent carcinoma has appeared in the adjacent trachea, esophagus, neurovascular bundles, and upper mediastinum It seems likely that this recurrent carcinoma represents continued growth of malignant tissue remaining after thyroidectomy. In the papillary group, 22 patients (12%) demonstrated local recurrence of papillary thyroid carcinoma in the thyroid region after periods ranging from three months to 28 years following thyroidectomy. The average

is assumed that the primary tumor has been completely removed surgically at the time of the first operation, it is apparent that metastases appearing months or years later originated following dissemination from the primary thyroid neoplasm before its surgical removal.

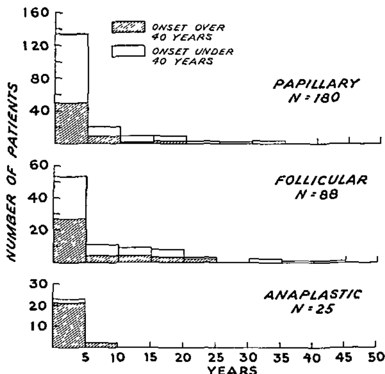
In the papillary group, 26 patients (14%) developed regional lymph node metastases two months or more following thyroidectomy. In 25 instances, the late metastases to regional lymph nodes occurred in the lateral cervical lymph nodes, and in one instance, in the mediastinal lymph nodes. Four patients had metastases in lymph nodes appear at two different intervals following operation, and one patient had metastatic lymph nodes appear on three separate occasions following the initial operation. The interval between operation and the later appearance of regional lymph node metastases varied from two months to 24 years, with an average interval of 4.9 years. Only one of these 26 patients has died of thyroid carcinoma.

Distant, later pulmonary metastases appeared in 10 patients (5%) with papillary carcinoma. Skeletal metastases, occurring later, were found in five patients (2%) These skeletal metastases occurred in the skull, ribs, sternum, spine, pelvis, and vertebras. Hepatic metastases were observed eventually in three patients. The interval between operation and the appearance of pulmonary metastases ranged from one to 10 years, with an average of 3.2 years. On the other hand, skeletal metastases appeared between five and 15 years after operation, with an average interval of 10 years. Of the 14 patients with distant metastases, 11 (78%) have died of thyroid carcinoma.

Of the total of 94 patients with papillary carcinoma who have displayed early or late, local or distant metastases, 19 had Grade I tumors and 75 had Grade II.

In the follicular group, nine patients (10%) had metastases in regional lymph nodes appear at intervals of one to nine years following operation (average, 2.4 years). In one instance, the metastases appeared in mediastinal lymph nodes; in the remainder, lateral cervical lymph nodes were involved. Only one patient with late cervical node metastases has died, but in that case, distant metastases were also present.

Table 53



rence in the opposite lobe following unilateral thyroid lobectomy. This would be expected, considering the high incidence of intraglandular lymphatic spread of papillary carcinoma to the opposite lobe Recurrence in the opposite lobe following unilateral lobectomy has not been observed in the patients with follicular or anaplastic carcinoma, in the present study

Death following local recurrence of all types of thyroid carcinoma resulted from the effects of local respiratory obstruction, and several patients also had exsanguinating tracheal hemorrhage from the neoplastic site.

Late Metastases in Thyroid Carcinoma

Local or distant metastases have also occurred later than at the time of the first thyroid operation in a considerable number of patients. Some, of course, had both early and later metastases. If it

local regional lymph node metastases appear at intervals between 0 and 34 years following the onset of goiter. The average interval was 4 9 years Distant metastases in patients with follicular carcinoma occurred in 15 patients at intervals ranging from 0 to 44 years (average, 14.2 years) following onset of goiter.

In the anaplastic group, six patients (20%) had early or late regional lymph node metastases at intervals ranging from 0 to 30 years following the onset of goiter, with an average of 7.8 years. Distant metastases occurred in nine (36%) patients at intervals ranging from 0 to 39 years (average, 13 years) following onset of goiter.

Age at Onset of Distant Metastases

In patients with each of the three types of thyroid carcinoma, distant metastases rarely appeared before 40 years of age (Table 54). This age incidence differs significantly from that of regional lymph node metastases (Table 47). Local metastases in lymph nodes from papillary and follicular carcinoma occur at any age, and in the papillary group, the highest incidence is in younger individuals.

Relation of Metastases in Regional Lymph Nodes and in *Distant Sites*

The relationship between local, regional, and distant metastases is shown in Table 55. This tabulation includes all patients with local and distant metastases, including lesions discovered during autopsy The incidence of distant metastases from each type of thyroid carcinoma is not significantly different in patients with or without regional lymph node metastases (papillary, $X_2 = 0.0248$; follicular, $X_2 = 1\ 0962$; and anaplastic, $X_2 = 2.1633$ with 1 df). This finding suggests that distant metastases are not likely to have originated in metastases in cervical lymph nodes, but rather in the primary thyroid neoplasm.

Duration of Metastatic Thyroid Carcinoma

The duration of life after the appearance of distant metastases from thyroid carcinoma is shown in Table 56.

Of the 180 patients with papillary carcinoma, 20 (11%) eventually had distant metastases. In five, the duration of the distant metastases was unknown, and in the remainder the duration

Sixteen patients with follicular carcinoma (22%) had late development of distant metastases, and all have died of thyroid carcinoma. Six patients (6%) developed pulmonary metastases at intervals of one to 11 years following operation (average 5.5 years). Twelve patients (13%) had skeletal metastases, appearing at intervals ranging from one to 20 years (average, 6.4 years) following thyroidectomy. These skeletal metastases involved the skull, ribs, sternum, vertebras, pelvis, and extremities. In addition, four patients had intracranial metastases, and one had hepatic metastases.

Of the 36 patients with follicular carcinoma who displayed early or late, local or distant metastases, 12 had Grade I neoplasms. The remaining 24 had Grade II or Grade III neoplasms.

In the anaplastic group, four patients (16%) had the late appearance of cervical lymph node metastases, at intervals ranging from 6 months to 10 years (average, 3.1 years) after thyroidectomy. Fourteen patients with anaplastic carcinoma had the late appearance of distant metastases.

Only three patients in the anaplastic group had skeletal metastases in the skull, humerus, pelvis, and femur, at intervals ranging from 18 months to 10 years (average, 4 3 years) following operation. More patients had metastases to soft tissues Pulmonary metastases occurred in six patients (24%) at intervals ranging from 6 months to seven years (average, 2 years) following operation. In addition, five patients had diffuse, widespread metastases, involving many organs and tissues, appearing at intervals between six months and two years (average, 1.5 years) following operation Of the 18 patients with anaplastic carcinoma who developed early or late, local or distant metastatic disease, 12 (66%) have died of anaplastic thyroid carcinoma All the neoplasms in this group were Grade III.

Interval Between Onset of Goiter and Appearance of Metastases

In the papillary group, 55 (30%) patients developed metastases in regional lymph nodes at intervals from 0 to 36 years (average, 2.1 years) following the onset of goiter. Six patients with papillary carcinoma developed distant metastases between 6 and 30 years after the onset of goiter, an average of 17 years.

Of the 88 patients with follicular carcinoma, 19 (21%) had

was unknown in four patients. The remaining 14 survived from two months to 12 years after the appearance of distant metastases. Two are alive one and six years, respectively, after the appearance of skeletal metastases

Survival of the 13 patients with metastatic anaplastic thyroid carcinoma was considerably shorter. In six patients the duration of pulmonary or generalized metastases was unknown. In the remaining seven, the duration of life after the appearance of distant metastases ranged from two to 11 months. Only one patient is alive seven years after the development of skeletal metastases.

Table 56

DURATION OF METASTATIC THYROID CARCINOMA

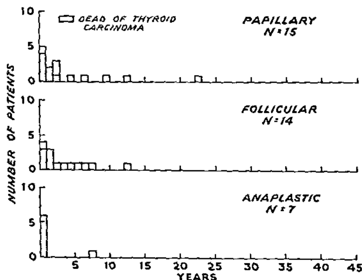
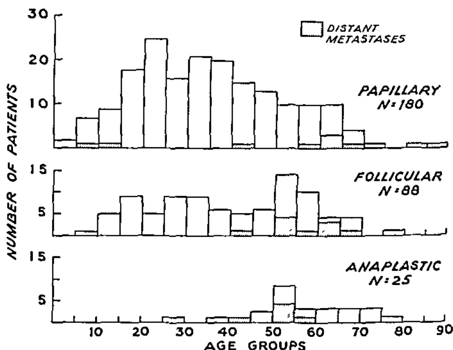


Table 54

AGE AT ONSET OF THYROID CARCINOMA AND AGE OF ONSET OF DISTANT METASTASES



of distant metastases ranged from two weeks to 22 years. Four patients with skeletal or pulmonary metastases are alive one to nine years after the appearance of these metastases.

Of the 88 patients with follicular carcinoma, 18 (20%) developed distant metastases. The duration of the distant metastases

Table 55

RELATION OF METASTASES IN REGIONAL LYMPH NODES AND DISTANT SITES

	Papillary (180)	*Follicular (88)*	*Anaplastic (25)*
Without node metastases Without distant metastases	82	50	7
With node metastases With distant metastases	11	3	9
Without node metastases With distant metastases	13	16	6
With node metastases Without distant metastases	74	9	3

these same 293 patients, designed to evaluate various forms of therapy in thyroid carcinoma (including both surgical therapy and external irradiation) are currently being made in this hospital (65). The disappointing results with internal irradiation with radioiodine in some of these patients have been reported by Sheline and Miller (66). At this hospital, surgical therapy of thyroid carcinoma has tended to become more radical during the past 10 years. Mediastinal dissection (67) has been included in this radical approach. Post-operative therapy with thyroid extract was administered to 95 of the 293 patients.

Chapter X

THERAPY OF THYROID CARCINOMA AT THE UNIVERSITY OF CALIFORNIA HOSPITAL

SINCE this report is not primarily concerned with the details or evaluation of surgical or radiological therapy in thyroid carcinoma, the therapy administered to the 293 patients at the University of California Hospital is merely summarized in Table 57. Studies of

Table 57

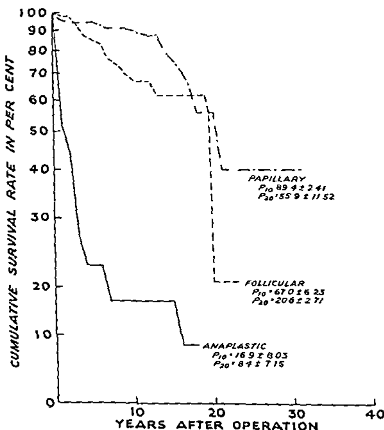
SURGICAL AND RADIOTHERAPY EMPLOYED IN 293 PATIENTS IN UNIVERSITY OF CALIFORNIA HOSPITAL

Surgical Therapy (Thyroid)			
Subtotal lobectomy			
	unilateral	52	
	bilateral	89	
	pyramidal lobe	1	
Total lobectomy			
	unilateral	37	
	bilateral	64	
Unilateral total and unilateral subtotal lobectomy		27	
Subtotal thyroidectomy followed by total		10	
Operation done elsewhere, type not known		9	
Biopsy		2	
Surgical Therapy (Regional lymph nodes)			
Local excision of all enlarged nodes		70	
Local excision (biopsy)		19	
Radical deep neck dissection			
	unilateral	30	
	bilateral	13	
Mediastinal dissection		7	(3 had positive nodes)
Surgical Therapy (Miscellaneous)			
Bilateral oophorectomy and adrenalectomy		1	
Radiotherapy			
External irradiation (including radium and radon)		71	
Internal irradiation (I_{131})		7	

percentages of patients with papillary and follicular carcinoma, surviving 10 years and 20 years after onset. There are significant differences, however, in survival at 10 years and 20 years after onset, between patients with papillary and anaplastic carcinoma and between patients with follicular and anaplastic carcinoma.

Table 59 shows the cumulative survival rates, after operation, for patients with the three major types of thyroid carcinoma. Significant differences in survival at 10 and 20 years after operation do not exist between patients with papillary and follicular carcinoma, but do exist between those with papillary and anaplastic

Table 59



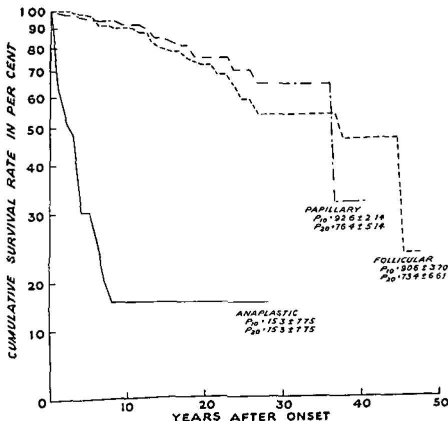
Chapter XI

SURVIVAL DATA ON PATIENTS WITH THYROID CARCINOMA

THE cumulative survival rates of patients after onset of papillary, follicular (all three subgroups), and anaplastic carcinoma are compared in Table 58. There are no significant differences between

Table 58

THYROID CARCINOMA
CUMULATIVE SURVIVAL RATE (FROM ONSET)



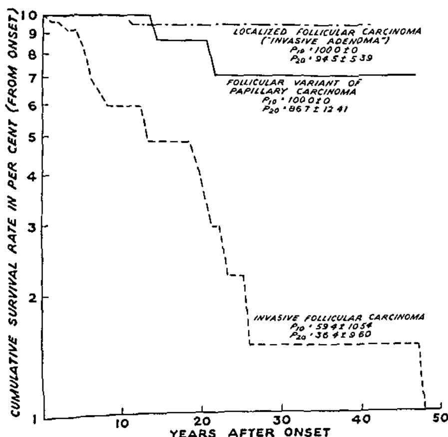
patients having the longer survival. Similar differences in survival exist at 20 years after onset, between patients with invasive follicular carcinoma and those with localized follicular carcinoma (invasive adenoma), the survival of patients with the latter neoplasm being distinctly longer. At 20 years, there appears to be no difference in survival between patients with the follicular variant of papillary carcinoma and those with localized follicular carcinoma.

Table 61 gives survival rates after operation of patients with the three subgroups of follicular carcinoma. At 10 years, the percentage surviving was higher for patients with the follicular variant of papillary carcinoma and for patients with localized follicular carcinoma than for those with invasive follicular carcinoma. No patients with the latter or with localized follicular carcinoma survived 20 years following operation. No significant differences in survival exist at 10 years and at 20 years after operation, between patients with the follicular variant of papillary carcinoma and with localized follicular carcinoma.

carcinoma, and between those with follicular and anaplastic carcinoma.

Table 60 compares survival after onset of patients with the three subgroups of follicular carcinoma. At 10 years after onset, there were no differences in survival between patients with localized follicular carcinoma and those with the follicular variant of papillary carcinoma. There were differences, however, in survival at 10 years, between patients with each of these two types of follicular carcinoma and those with invasive follicular carcinoma (SE = 0%). There were significant differences in survival at 20 years after onset, between patients with invasive follicular carcinoma and those with the follicular variant of papillary carcinoma, the latter

Table 60



There were no significant differences in survival between males and females with papillary and follicular carcinoma at 10 years and 20 years after onset of thyroid carcinoma or after operation (Tables 62, 63, 64, and 65). No males (three patients) with anaplastic carcinoma survived 10 years or 20 years after onset of the disease or after operation (Tables 66 and 67).

Table 62

PAPILLARY CARCINOMA IN MALES AND FEMALES

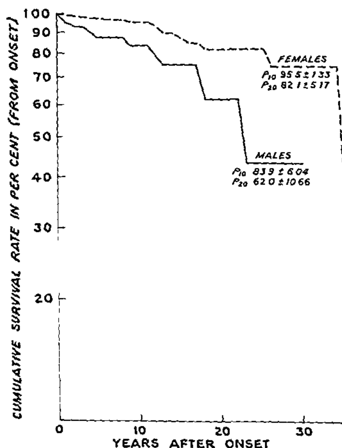


Table 61

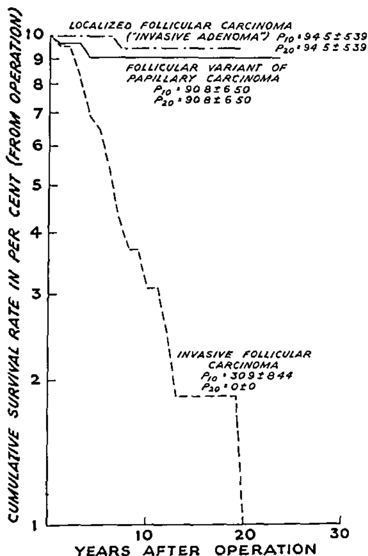

FOLLICULAR CARCINOMA (3 TYPES)
LOCALIZED FOLLICULAR CARCINOMA
("INVASIVE ADENOMA") P_{10} = 94 5 ± 5 39
P_{20} = 94 5 ± 5 39
FOLLICULAR VARIANT OF
PAPILLARY CARCINOMA
P_{10} = 90 8 ± 6 50
P_{20} = 90 8 ± 6 50
INVASIVE FOLLICULAR
CARCINOMA
P_{10} = 30 9 ± 8 44
P_{20} = 0 ± 0
CUMULATIVE SURVIVAL RATE IN PER CENT (FROM OPERATION)
10
9
8
7
6
5
4
3
2
1
10
20
30
YEARS AFTER OPERATION

Table 64

FOLLICULAR CARCINOMA IN MALES AND FEMALES

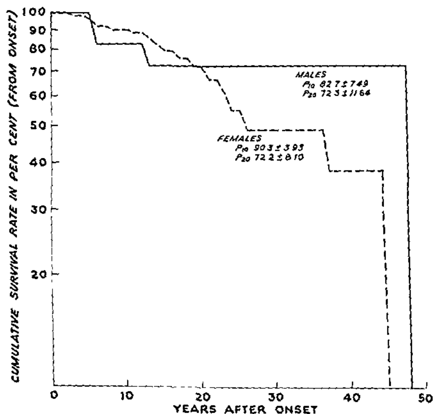


Table 63

PAPILLARY CARCINOMA IN MALES AND FEMALES

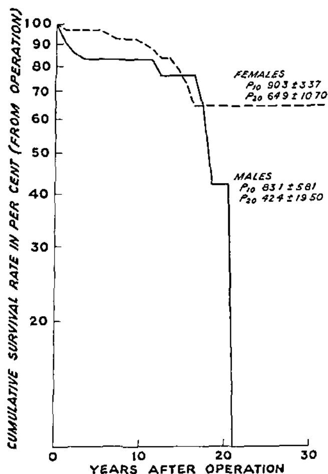


Table 66

ANAPLASTIC CARCINOMA IN MALES AND FEMALES

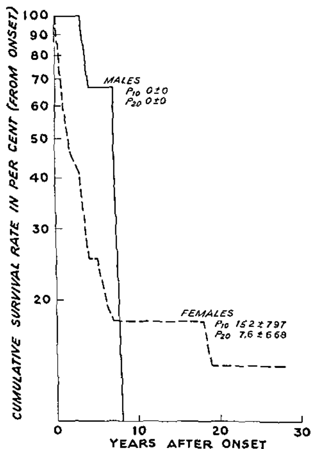


Table 65

FOLLICULAR CARCINOMA IN MALES AND FEMALES

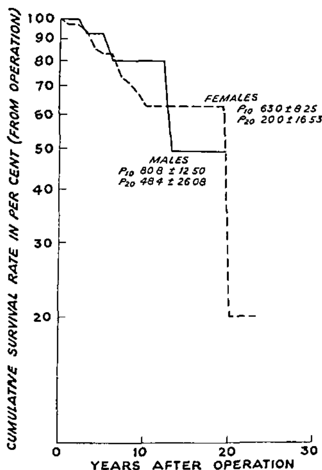


Table 66

ANAPLASTIC CARCINOMA IN MALES AND FEMALES

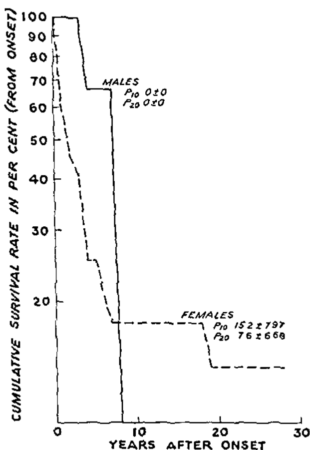
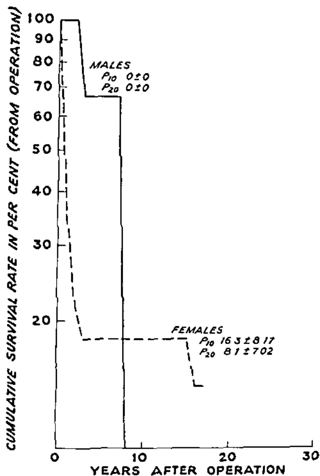


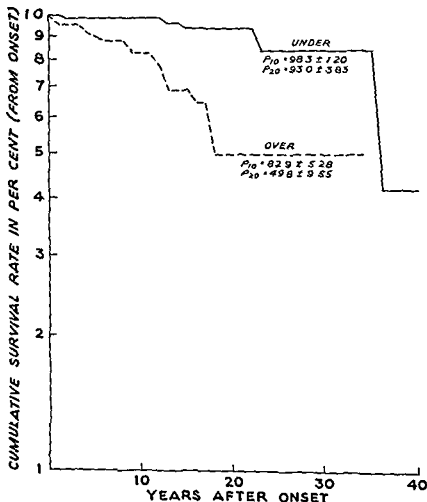
Table 67

ANAPLASTIC CARCINOMA IN MALES AND FEMALES



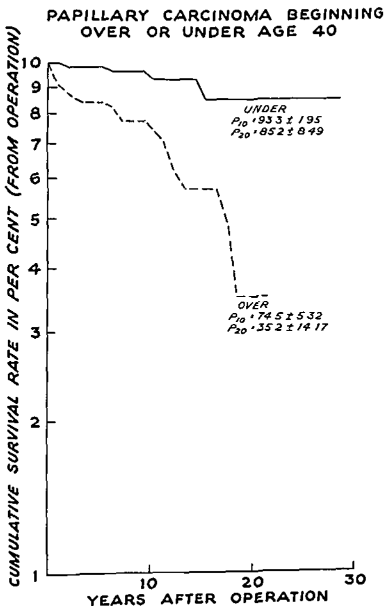
A comparison of survival rates of patients with papillary carcinoma beginning under or over the age of 40 years is shown in Tables 68 and 69. Both at 10 years and at 20 years after the onset of disease and after operation, the percentage of surviving patients

Table 68



whose thyroid malignancy began under the age of 40 years was significantly higher than the percentage of those whose disease began over the age of 40.

Table 69



In Tables 70 and 71, the survival of patients with follicular carcinoma originating under and over the age of 40 years is compared. The percentage surviving for 10 years and 20 years from onset of the disease was higher in those whose disease began under the age of 40 (Table 70). At 10 years following operation, a higher percentage of patients with disease beginning under 40 years survived than of patients with disease beginning over the age of 40. At 20 years following operation, no patients with disease beginning over age 40 survived, whereas 39.6% of patients whose disease began under the age of 40 years survived 20 years (Table 71).

Table 70

FOLLICULAR CARCINOMA BEGINNING OVER OR UNDER AGE 40

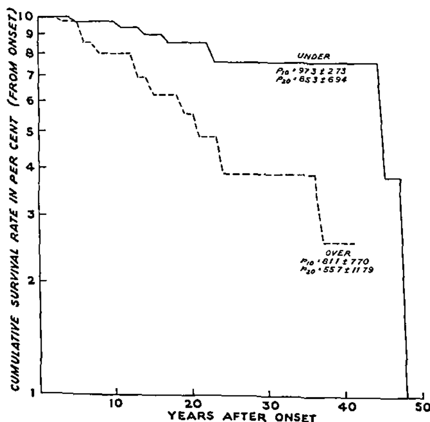
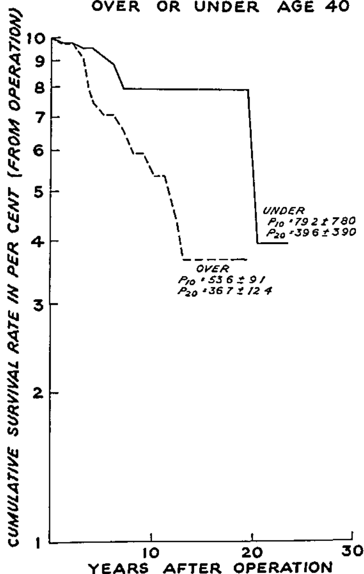


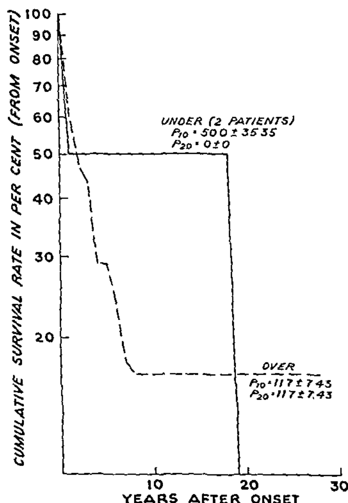
Table 71

FOLLICULAR CARCINOMA BEGINNING OVER OR UNDER AGE 40



Tables 72 and 73 show the cumulative survival rates of patients with anaplastic carcinoma beginning under or over the age of 40 years, calculated both from the time of onset of disease and from operation. At 10 years after onset and at 10 years after operation, there were no significant differences in percentage of surviving

Table 72



patients whose disease began under or over the age of 40 years. None of the patients with anaplastic carcinoma survived 20 years after onset or 20 years after operation.

Table 73

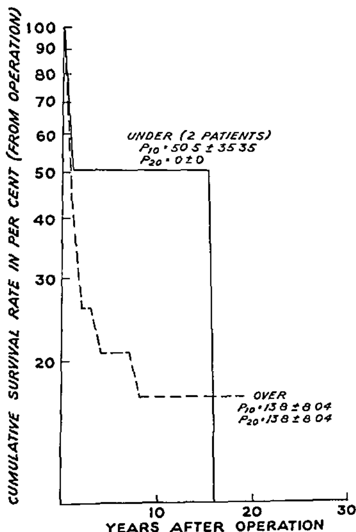


Table 74 compares the cumulative survival rates, after operation, of patients with papillary carcinoma, first diagnosed clinically during operation or in the pathologic laboratory. At 10 years after operation, the percentage of patients surviving who were first diagnosed at surgery was higher than the percentage first diagnosed clinically. None of the patients diagnosed first at surgery was followed 20 years after operation, whereas 40.9% of those diagnosed clinically survived 20 years following operation At 10 years after operation, a higher percentage of patients whose neoplasm was first diagnosed by histologic examination survived than was the case with those whose diagnosis was made clinically. The percentage of patients surviving 20 years after operation, who were diagnosed pathologically, was higher than that of patients diagnosed clinically, but the differences were not statistically significant. Comparing survival of those diagnosed first at surgery and in the laboratory, there were no differences at 10 years following operation. At 20 years, 72.2% of the patients diagnosed histologically survived, while none diagnosed at operation was followed for 20 years. These data indicate that the papillary carcinomas first diagnosed pathologically were probably small, incidental lesions as compared with those that were obviously malignant clinically. As expected, the patients with papillary carcinomas who were first diagnosed during surgery survived longer than those first diagnosed clinically.

Table 74

PAPILLARY CARCINOMA - DIAGNOSIS MADE CLINICALLY, SURGICALLY, OR PATHOLOGICALLY

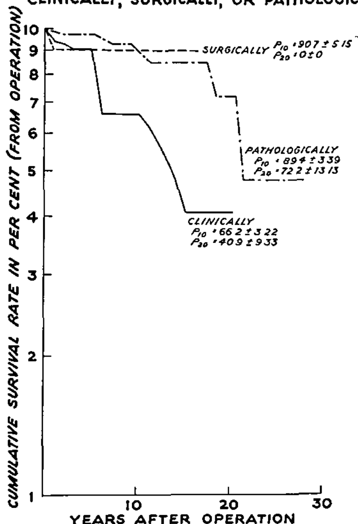
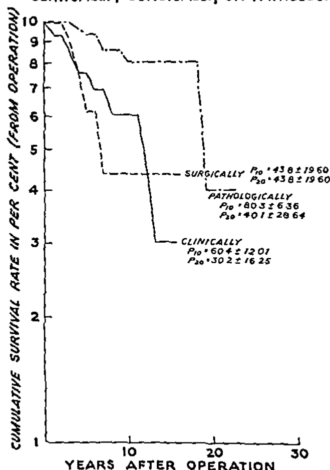


Table 75 compares survival rates of patients with follicular carcinoma first diagnosed, either clinically, at operation, or pathologically. There were no significant differences in survival rates at 10 years or at 20 years in these three groups of patients.

All anaplastic carcinomas were diagnosed either clinically or at

Table 75



operation. There were no significant differences in survival 10 years following operation, between the two types of diagnoses (Table 76). None of either group survived 20 years following surgery.

Table 76

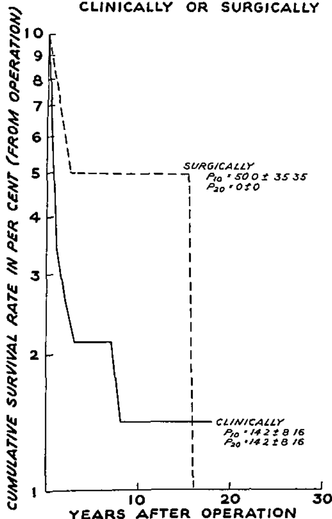


Table 77 compares survival of patients with papillary carcinoma, having primary thyroid neoplasms over or under 2 cm. in diameter. At 10 years after onset, 100% of patients with tumors under 2 cm. survived (SE = 0%), and 90.9% of patients with neoplasms over 2 cm. were alive. There was no significant difference at 20 years, of percentages of patients surviving with neoplasms under or over 2 cm.

Table 77

DURATION OF PAPILLARY CARCINOMA TUMOR OVER OR UNDER 2 CM.

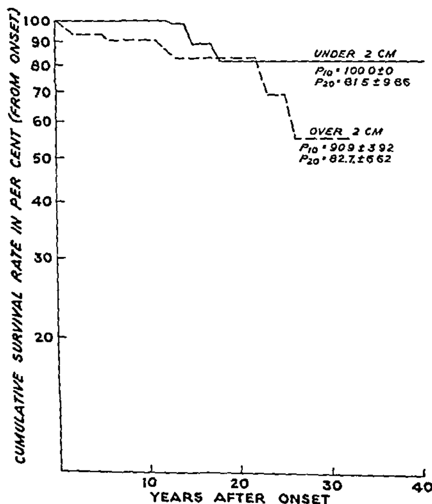


Table 78 shows post-operative survival rates of patients with papillary carcinomas under and over 2 cm. At 10 years after operation, the survival of patients with tumors under 2 cm. was 94.6% (SE = 0%); of those with tumors over 2 cm., 86 9%. There was no significant difference in percentage survival between the two groups at 20 years following operation

Table 78

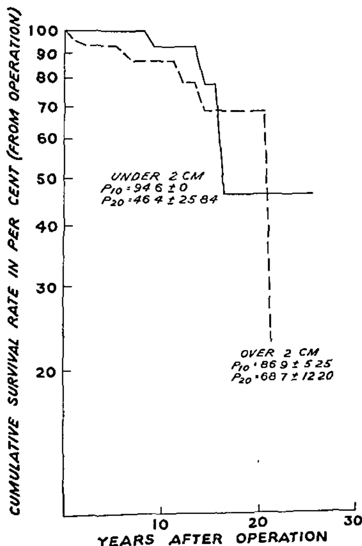
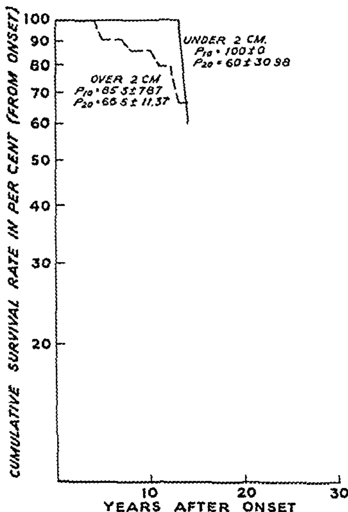


Table 79 shows survival of patients with follicular carcinoma after onset of the disease, comparing those with primary neoplasms under and over 2 cm. At 10 years after onset, 100% of patients with neoplasms under 2 cm. survived (SE = 0%), as compared

Table 79



with 85.3% with neoplasms over 2 cm. There were no significant differences in survival of the two groups at 20 years after onset.

Differences in survival after operation, of patients with follicular carcinoma with primary tumors under and over 2 cm. are shown in

Table 80

DURATION OF FOLLICULAR CARCINOMA
TUMOR OVER OR UNDER 2 CM.

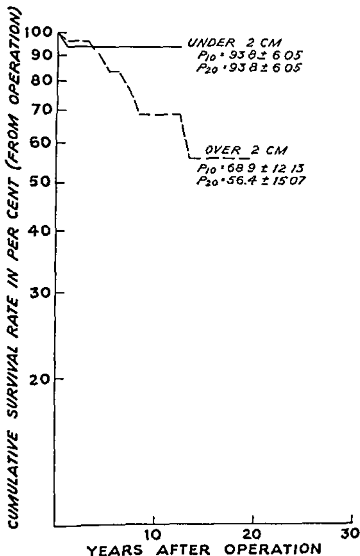


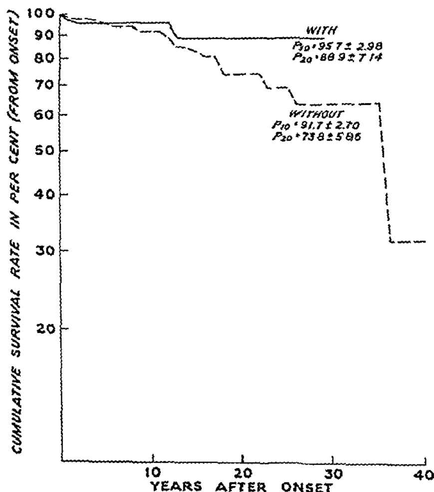
Table 80. At 10 years and at 20 years following operation, a higher percentage of patients with primary neoplasms under 2 cm. survived than was the case of those with neoplasms over 2 cm.

No patients with anaplastic carcinoma had primary thyroid neoplasms measuring less than 2 cm.

In Table 81, survival rates of patients with papillary carcinomas

Table 81

PAPILLARY CARCINOMA
WITH AND WITHOUT PSAMMOMA BODIES

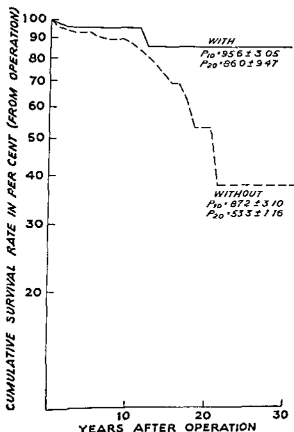


with or without psammoma bodies are compared. Survival to 10 years and to 20 years after onset was not significantly different in the two groups.

Post-operative survival rates of patients with papillary carcinoma, with or without psammoma bodies showed no significant differences between the two groups after 10 years (Table 82). At 20 years, however, the percentage of surviving patients whose neoplasm contained psammoma bodies was significantly higher than that of those without psammoma bodies. This finding is consistent with the observation that psammoma bodies are generally found in those papillary carcinomas which are well-differentiated.

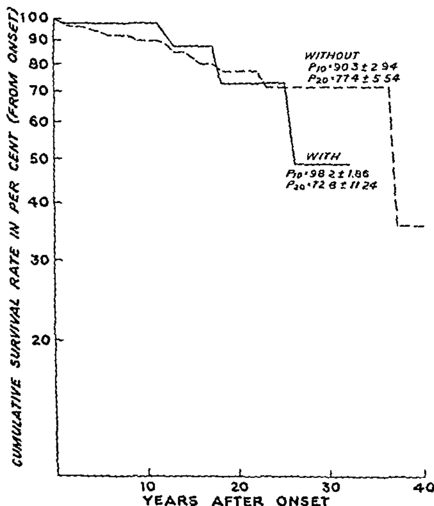
Table 82

PAPILLARY CARCINOMA
WITH AND WITHOUT PSAMMOMA BODIES



In Table 83 are shown cumulative survival rates, from the time of onset of disease, of patients with papillary carcinoma, with or without associated Hashimoto disease. At 10 years after onset, the percentage of survival of patients with Hashimoto disease was significantly higher than the percentage of those surviving without

Table 83



Hashimoto disease. At 20 years, however, there were no significant differences in survival between the two groups. The percentages of patients with papillary carcinoma with and without Hashimoto disease surviving after operation showed no significant differences at 10 years and at 20 years (Table 84).

Table 84

PAPILLARY CARCINOMA
WITH AND WITHOUT HASHIMOTO DISEASE

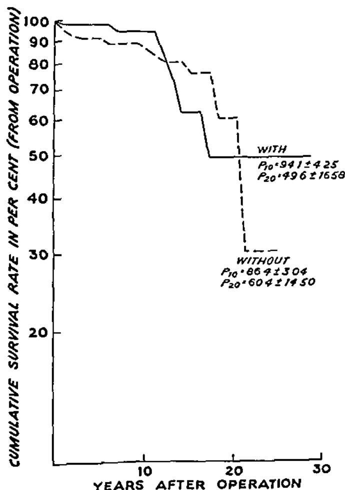
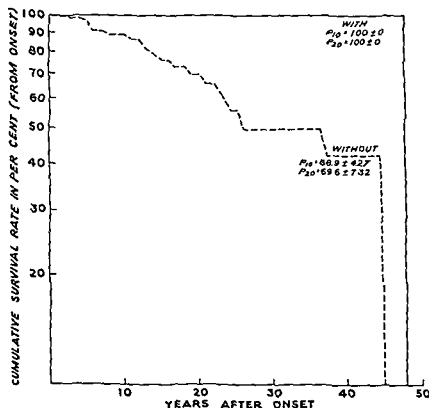


Table 85 shows cumulative survival rates, after the onset of disease, of patients with follicular carcinoma with and without Hashimoto disease. There was 100% (SE = 0%) survival at 10 and 20 years of patients with associated Hashimoto disease. The percentage of those without associated Hashimoto disease surviving 10 years was 88.9 (SE = 4.27%), and at 20 years, 69.6 (SE = 7.32%).

Post-operative survival of patients with follicular carcinoma (Table 86) with and without Hashimoto disease showed no significant differences at 10 years. At 20 years, however, a signifi-

Table 85

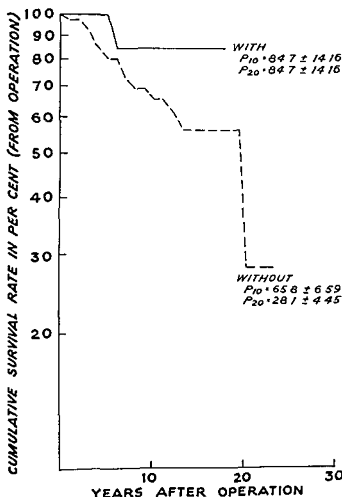
FOLLICULAR CARCINOMA
WITH AND WITHOUT HASHIMOTO DISEASE



cantly higher percentage of patients with associated Hashimoto disease survived.

Since the survival rates of patients with papillary carcinoma associated with Hashimoto disease were not consistently different, at 10 and 20 years after onset and after operation, from those with

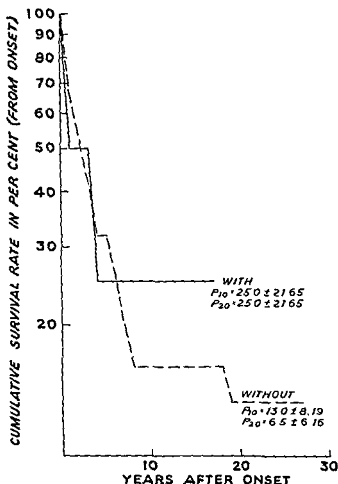
Table 86



papillary carcinoma without Hashimoto disease, it seems unlikely that the presence of the Hashimoto process confers any restraining influence on the malignant papillary process (68). There is more evidence, however, that patients with follicular carcinoma associated with Hashimoto disease survive longer than those with follicular carcinoma without Hashimoto disease. It should be noted

Table 87

ANAPLASTIC CARCINOMA
WITH AND WITHOUT HASHIMOTO DISEASE

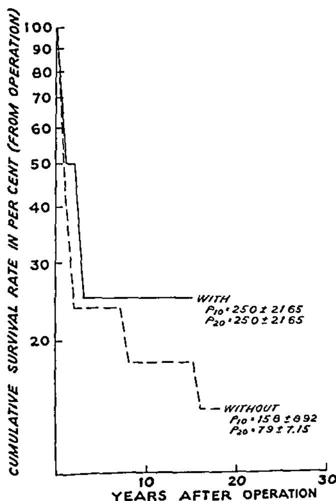


that a number of small carcinomas (both papillary and follicular) seen only on microscopic examination were found in enlarged thyroid glands removed because of Hashimoto disease.

There were no significant differences in survival rates of patients with anaplastic carcinoma, with and without associated Hashimoto disease, at 10 years or 20 years after onset or after operation (Tables 87 and 88).

Table 88

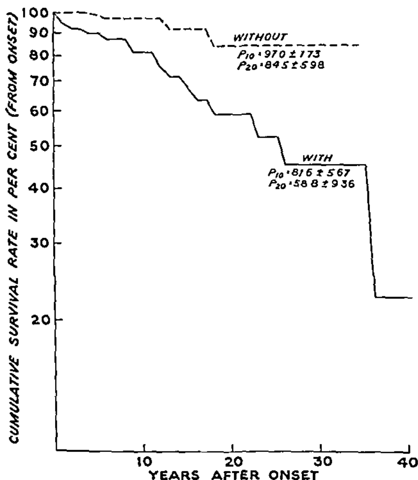
ANAPLASTIC CARCINOMA
WITH AND WITHOUT HASHIMOTO DISEASE



In Table 89 are shown the cumulative survival rates, from the time of onset of the disease, of patients with papillary carcinoma with and without evidence, at operation, of extraglandular invasion.

Table 89

PAPILLARY CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION

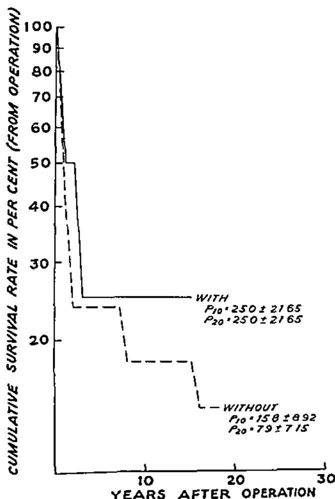


that a number of small carcinomas (both papillary and follicular) seen only on microscopic examination were found in enlarged thyroid glands removed because of Hashimoto disease.

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Table 88

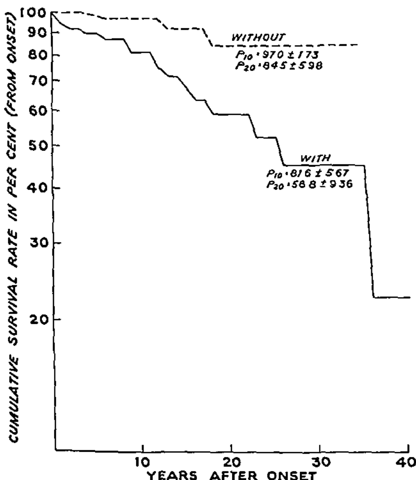
ANAPLASTIC CARCINOMA
WITH AND WITHOUT HASHIMOTO DISEASE



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Table 89

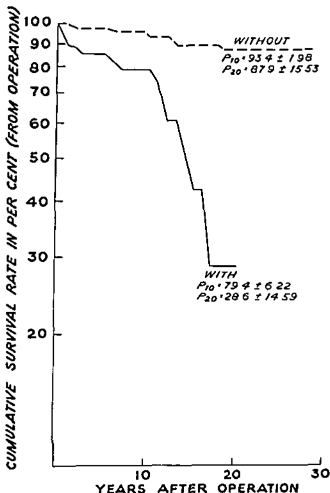
PAPILLARY CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION



The percentage surviving without extraglandular invasion was significantly higher at 10 and at 20 years both after onset and after operation (Table 90).

Table 90

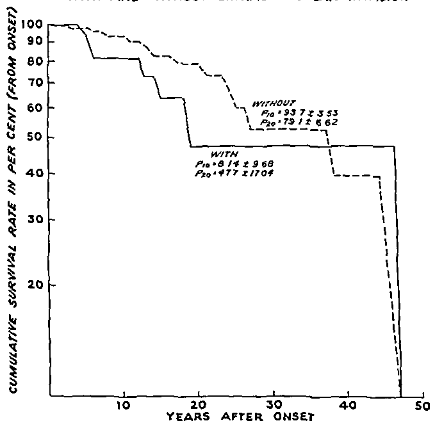
PAPILLARY CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION



Tables 91 and 92 show survival of patients with follicular carcinoma with and without evidences of extraglandular invasion at the time of operation. There were no significant differences in the percentages of either group surviving 10 years and 20 years after onset or after operation.

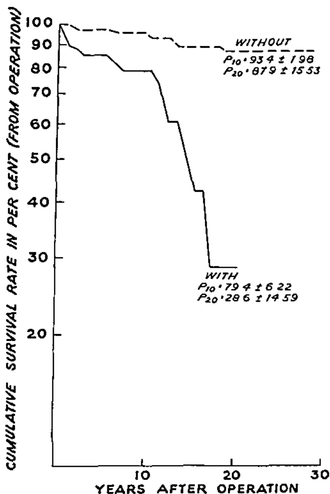
Table 91

FOLLICULAR CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION



The percentage surviving without extraglandular invasion was significantly higher at 10 and at 20 years both after onset and after operation (Table 90).

Table 90



Tables 91 and 92 show survival of patients with follicular carcinoma with and without evidences of extraglandular invasion at the time of operation. There were no significant differences in the percentages of either group surviving 10 years and 20 years after onset or after operation.

Table 91

FOLLICULAR CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION

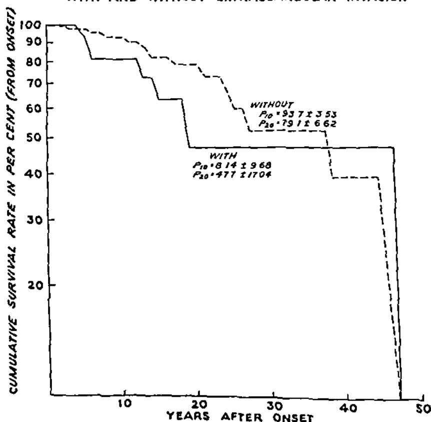
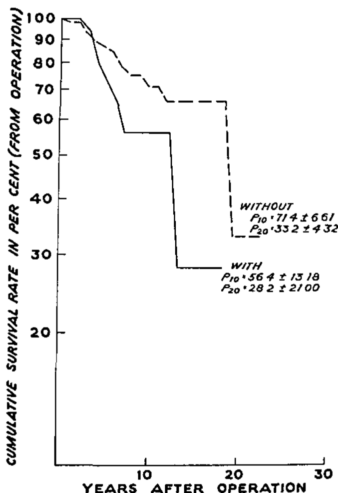
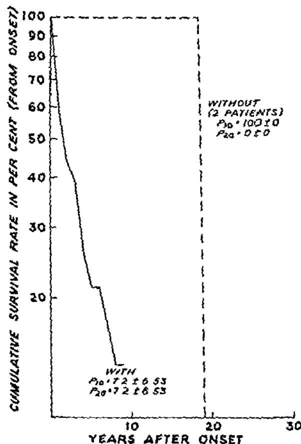


Table 92


FOLLICULAR CARCINOMA
WITH AND WITHOUT EXTRAGLANDULAR INVASION
CUMULATIVE SURVIVAL RATE IN PER CENT (FROM OPERATION)
100
90
80
70
60
50
40
30
20
WITHOUT
P_{10} · 71 4 ± 6 61
P_{20} · 33 2 ± 4 32
WITH
P_{10} · 56 4 ± 13 18
P_{20} · 28 2 ± 21 00
10
20
30
YEARS AFTER OPERATION

There were only two patients without extraglandular invasion in the anaplastic group and both survived 10 years after onset. None of the anaplastic patients with extraglandular invasion survived after 10 years following onset (Table 93). Post-operative survival of patients with anaplastic carcinoma with and without extraglandular invasion is shown in Table 94. Two patients (100%) without extraglandular invasion survived 10 years after operation, as compared with only 8.4% of those with extraglandular invasion. None

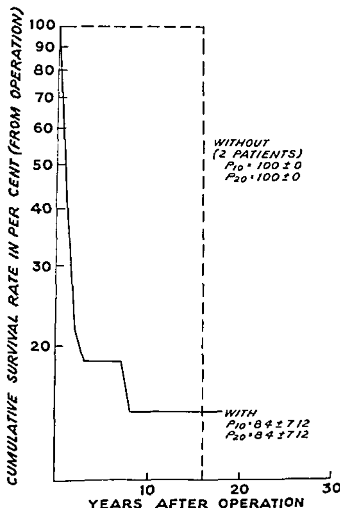
Table 93



of the latter survived 20 years after operation.

These data on papillary and anaplastic carcinoma are consistent with the concept that a malignant neoplasm which has escaped beyond the organ in which it originated is less likely to be cured than one which is localized. Since follicular carcinomas character-

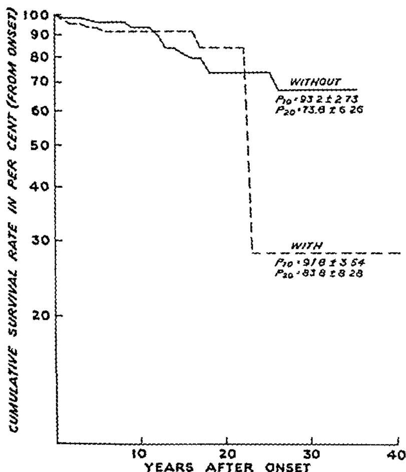
Table 94



istically metastasize through blood vessels, this mode of dissemination may be of greater prognostic significance in follicular carcinoma than is local extraglandular invasion. Tables 95 and 96 show survival, from onset and from operation, of patients with papillary carcinoma with or without regional lymph node metastases at the time of first operation. There were no differences between the percentage of patients surviving with or without

Table 95

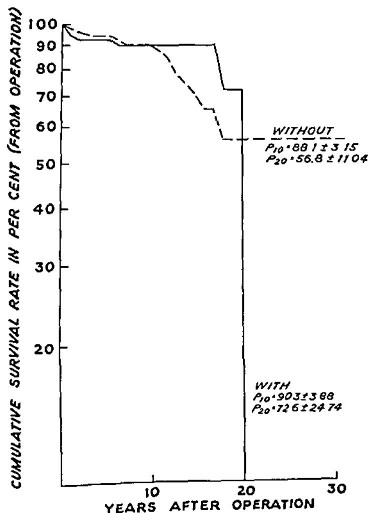
PAPILLARY CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



regional lymph node metastases 10 or 20 years after onset or after operation. These data are of considerable interest, especially in the light of the current controversy concerning appropriate surgical therapy of thyroid carcinoma, particularly of the papillary variety. The data should be interpreted cautiously, however, since the patients with cervical lymph node metastases had some type of excision of cervical lymph nodes, either simple or radical. This

Table 96

PAPILLARY CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES

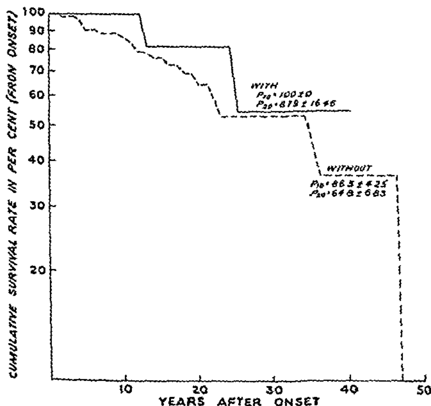


surgical removal of cervical lymph nodes involved with papillary cancer may account for the lack of significant differences in survival of the two groups.

Table 97 shows survival, after onset, of patients with follicular carcinoma with and without lymph node metastases at the time of operation. At 10 years after onset, 100% (SE = 0%) of patients with lymph node metastases survived, as compared with 83.8% (SE = 4.25%) of those without lymph node metastases. At 20 years, 81.9 and 64.8%, respectively, of patients with and without lymph node metastases survived The percentages of patients in each group surviving 20 years were not significantly different.

Table 97

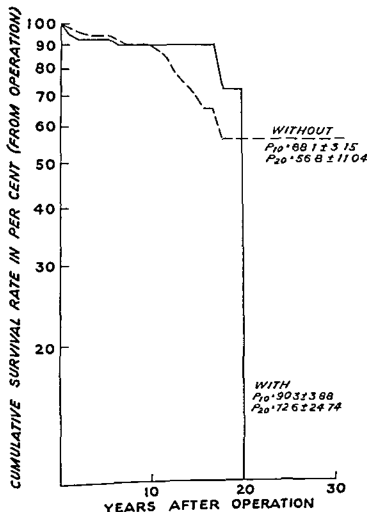
FOLLICULAR CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



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Table 96

PAPILLARY CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



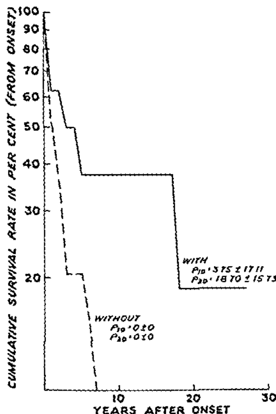
cervical lymph nodes (Table 27), and had a higher survival rate than invasive follicular carcinoma (Tables 60 and 61). Or surgical removal of the involved nodes may account for longer survival, but this explanation seems less probable.

None of the patients with anaplastic carcinoma without lymph node metastases survived 10 or 20 years after onset (Table 99).

Post-operative survival of patients with anaplastic carcinoma with and without regional lymph node metastases is shown in Table

Table 99

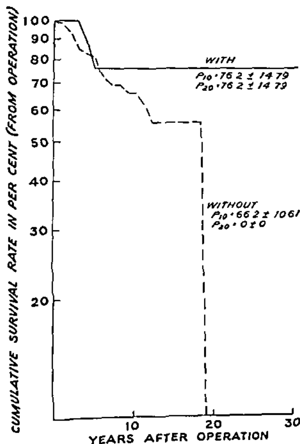
ANAPLASTIC CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



In Table 98, post-operative survival rates of patients with follicular carcinoma with or without regional lymph node metastases are compared. There was no significant difference in survival between the two groups at 10 years. At 20 years, 76.2% (SE = 14.79%) with lymph node metastases survived, whereas none without lymph node metastases was living. This finding seems paradoxical. However, since true invasive follicular carcinoma does not commonly metastasize to regional lymph nodes (Table 27), the patients surviving longer with lymph node metastases may be those with the follicular variant of papillary carcinoma which (like papillary carcinoma) characteristically and commonly metastasizes to

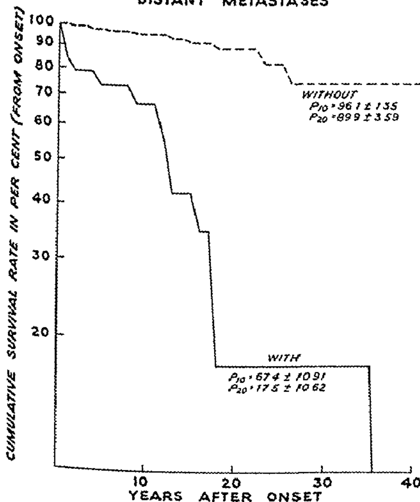
Table 93

FOLLICULAR CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



Survival after onset and after operation, of patients with papillary carcinoma with or without distant metastases is shown in Tables 101 and 102. Both at 10 years and at 20 years after onset and after operation, a significantly higher percentage of patients without distant metastases survived.

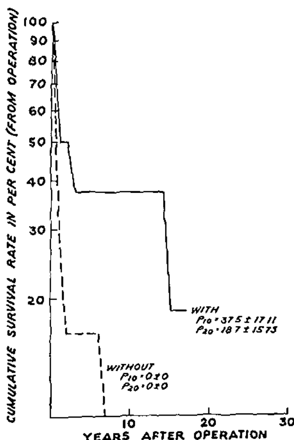
Table 101



100. None of the patients without lymph node metastases survived 10 years, and none with lymph node metastases survived 20 years after operation. The rapidly growing anaplastic carcinomas caused death by local growth before metastases in regional lymph nodes occur. The more slow-growing, less aggressive, anaplastic carcinomas are more likely to metastasize to regional nodes, and patients with these neoplasms survive longer.

Table 100

ANAPLASTIC CARCINOMA
WITH AND WITHOUT REGIONAL LYMPH NODE METASTASES



In Table 103 are shown cumulative survival rates, after onset, of patients with follicular carcinoma with and without distant metastases. At 10 years after onset, the percentage survivals of both groups were not significantly different. At 20 years after onset, however, the percentage of patients surviving without distant metastases was significantly higher.

Post-operative survival of patients with follicular carcinoma is

Table 103

FOLLICULAR CARCINOMA WITH AND WITHOUT DISTANT METASTASES

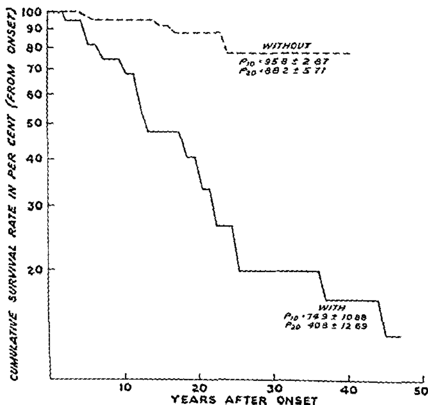
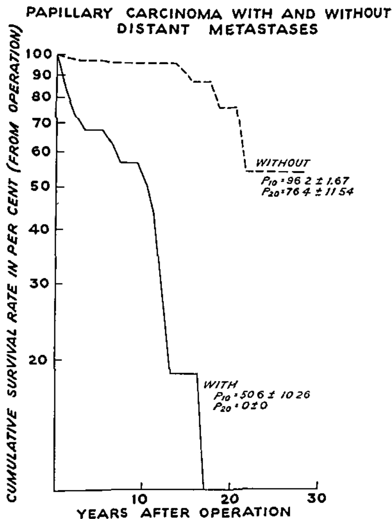
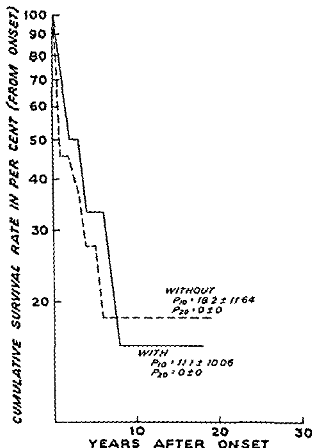


Table 102


PAPILLARY CARCINOMA WITH AND WITHOUT DISTANT METASTASES
CUMULATIVE SURVIVAL RATE IN PER CENT (FROM OPERATION)
100
90
80
70
60
50
40
30
20
WITHOUT
P10 = 96 2 ± 1.67
P20 = 76 4 ± 11 54
WITH
P10 = 50 6 ± 10 26
P20 = 0 ± 0
10
20
30
YEARS AFTER OPERATION

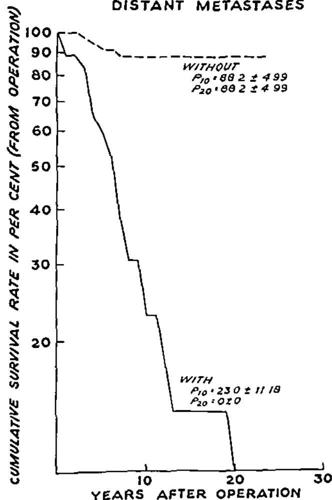
In tables 105 and 106 are shown cumulative survival rates of patients with anaplastic carcinoma, from onset and from operation, with and without distant metastases. At 10 years after onset and after operation, there were no significant differences in survival

Table 105



shown in Table 104. Ten-year survival without distant metastases was significantly higher than with distant metastases. No patients with distant metastases were alive 20 years after operation, whereas 88 2% of those without distant metastases had survived.

Table 104



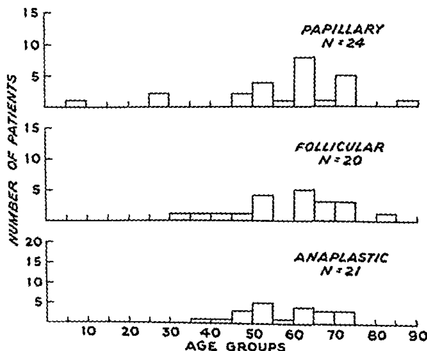
Chapter XII

DEATH FROM THYROID CARCINOMA

Of the 293 patients in this study, 65 (22%) have died of thyroid carcinoma (papillary, 24 (13%); follicular, 20 (22%); and anaplastic, 21 (84%). Their age at death is shown in Table 107. Only three patients with papillary carcinoma have died before the age of 45 years. One patient, age 7, died postoperatively from accidental obstruction of a tracheotomy tube. Two other patients, age 26 and 29, respectively, died of pulmonary and other widespread metastases. Although the incidence of papillary carcinoma

Table 107

AGE AT DEATH FROM THYROID CARCINOMA



of patients in the two groups. No patients with anaplastic carcinoma survived 20 years after onset or after operation. These data are consistent with the observation that more deaths from thyroid carcinoma result from distant metastases than from local cervical growth and respiratory obstruction.

Table 106

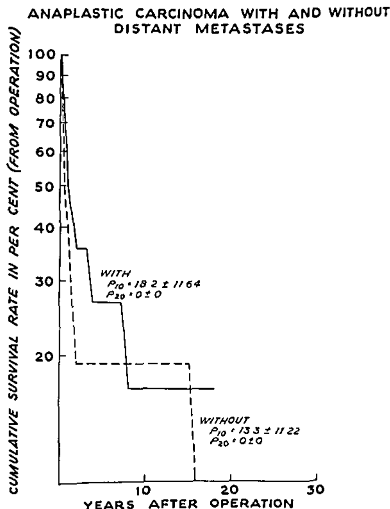
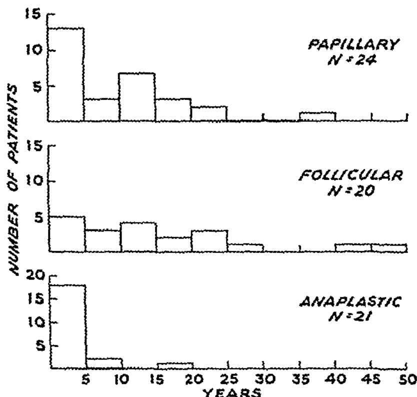


Table 109



anaplastic carcinoma is distinctly shorter. Of the 21 patients dead with anaplastic carcinoma, 16 died within one year following operation.

Of the 65 patients dead of thyroid carcinoma, only 10 have been subjected to autopsy examination at the University of California Hospital since 1941. The autopsy rate for thyroid carcinoma at this hospital from 1941 to 1954 has been shown to be approximately 1 in 252 autopsies. The majority of patients in this study died at home or in other hospitals (where several autopsies were performed) The clinical information obtained from the patients' physicians or from death certificates was adequate in determining the immediate cause of death.

is higher in the younger age groups, death from this form of thyroid carcinoma rarely occurs until past middle age. An essentially similar distribution of ages at death from follicular carcinoma is noted. The majority of patients with anaplastic carcinoma die after the age of 50 years. Frazell and Duffy (69) have reported that approximately 20% of their patients with papillary carcinoma, with long term follow-up, were dead of that disease. These authors stressed the importance of recognition of the delayed aggressive characteristics of papillary carcinoma.

The number of deaths in males and females with each type of thyroid carcinoma is shown in Table 108. Significantly more males than females have died of papillary carcinoma ($X_2 = 5.18$ with 1 df). There were no significant differences in numbers of deaths in males and females from follicular ($X_2 = 0.473$) or from anaplastic ($X_2 = .762$ with 1 df) carcinoma.

Table 108

DEATHS IN MALES AND FEMALES FROM THYROID CARCINOMA

	Male	*Female*	*Total*	
PAPILLARY	11	13	M	45
			F	135
FOLLICULAR	3	17	M	18
			F	70
ANAPLASTIC	2	19	M	3
			F	22
				293

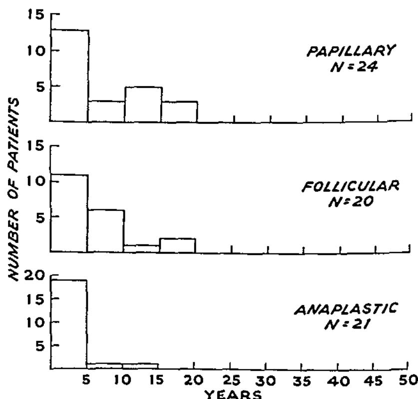
Table 109, showing the duration of thyroid carcinoma from onset to death, indicates that papillary and follicular carcinomas, eventually fatal, are compatible with long periods of survival. A few patients with fatal follicular carcinoma survived even longer after onset than those with fatal papillary carcinoma. Anaplastic carcinoma, however, characteristically, has a short duration, with death occurring within five years after onset in most patients. Actually, 12 of the 21 patients dead of anaplastic carcinoma died one year or less from the clinical onset of the disease. In Table 110, showing the duration of fatal carcinoma from operation to death, the survival of patients with papillary and follicular carcinoma is seen to be similar. Survival from time of operation in

died of respiratory obstruction, and one of these also had extensive distant metastases. Thirteen (61%) died of distant metastases, and one of these also had severe hemorrhage from the operative site terminally. One patient with anaplastic carcinoma died as a result of invasion of a carotid artery followed by carotid thrombosis and cerebral embolism.

Histologic and Cytologic Patterns of Metastatic Thyroid Carcinoma Observed at Autopsy

Of the 10 patients on whom autopsies were performed, six died of papillary carcinoma, and of these, three died of multiple distant metastases three months to 20 years after thyroidectomy. In these three patients, the pulmonary and other metastases had histologic and cytologic patterns distinctly different from those of the original primary thyroid neoplasms which were moderately well-differentiated papillary carcinomas. The metastases consisted mainly of extremely pleomorphic, multinucleated, epithelial cells having hyperchromatic nuclei. Many cells were spindle-shaped, and mitoses were numerous. In one patient, the cells were similarly pleomorphic but were Hürthle-like, and possessed abundant eosinophilic cytoplasm In only one patient did the metastatic lesions contain a few areas of more differentiated neoplastic tissue consisting of more uniform cells having a lobular pattern In another patient, the anaplastic pulmonary metastases which had been present for 22 years contained psammoma bodies, but no differentiated papillary tissue remained These pulmonary metastases had become smaller after intensive therapy with radioiodine (66). Of the three other patients dying of papillary carcinoma, one had local recurrence of a highly anaplastic neoplasm, whereas the original neoplasm in the thyroid gland had been a well-differentiated papillary carcinoma Another patient, a child of 7 years who died from accidental obstruction of a tracheotomy tube shortly after operation, had a single, tiny pulmonary metastasis observed microscopically The pattern of this lesion was identical with that of the primary thyroid neoplasm. Another patient who died eight days postoperatively had no distant metastases, but displayed direct extension of the thyroid carcinoma into the mediastinum. Those invasive portions of the neoplasm in the chest most distant from the thyroid gland showed a distinctly more pleomorphic pattern

Table 110



Immediate Cause of Death from Thyroid Carcinoma

In the papillary group, seven deaths (29%) were due to local cervical growth of the neoplasm with resulting respiratory obstruction. In two of these cases, the obstruction was associated with severe, exsanguinating hemorrhage. Fifteen patients (62%) died of distant metastases, and one died presumably from both respiratory obstruction and distant metastases. One patient died of hemorrhage from post-irradiation necrosis of cervical tissue.

In the follicular group, four patients (20%) died of respiratory obstruction, and in one of these there were severe exsanguinating hemorrhage and distant metastases. Sixteen patients (80%) with fatal follicular carcinoma died of extensive distant metastases, as discussed in the previous section of this report.

Of 21 patients dying from anaplastic carcinoma, seven (33%)

Chapter XIII

CONCLUSIONS

Prevention of Thyroid Carcinoma

DURING recent years, most discussions concerned with prevention of thyroid carcinoma have revolved about the question of prophylactic surgical removal of nodular goiters. The results of the present study indicate that few thyroid carcinomas arise in previously benign thyroid nodules. True, most thyroid carcinomas make their appearance as thyroid nodules, usually single, but the finding of varying percentages of malignant neoplasms in series of nodular goiters (11) does not prove that thyroid carcinomas arise in benign nodular goiters Nor does it follow that wholesale removal of nodular goiters will prevent later development of thyroid carcinoma. Although certain clinical manifestations suggest that a thyroid nodule may be malignant (50, 51, and 52), many malignant thyroid nodules can be distinguished from benign nodules only by microscopic examination. Whether or not a nodular goiter should be removed surgically should be determined by the physician for the individual patient. Nodular goiters in children, young individuals, and in older males are to be regarded with real suspicion.

The occurrence of a significant epithelial proliferative reaction in Hashimoto disease (23) and the histologic and statistical relationships between Hashimoto disease and thyroid carcinoma observed previously (22) and in the present study, indicate that Hashimoto disease may be a premalignant process Recent important developments in the study of Hashimoto disease (70, 71) have demonstrated, however, that auto-immunity to thyroglobulin plays a role in the pathogenesis of this disease, and that thyroid enlargement in the disease can be reversed by administration of thyroid extract Whether such therapy will reverse the epithelial proliferation, which is possibly premalignant, remains to be seen.

Studies reported thus far indicate that some thyroid carcinomas may be prevented by restraint in subjecting the thyroid gland to

with nuclear hyperchromatism and mitotic activity than did the primary neoplasm within the thyroid gland.

Autopsies were performed on two patients who died from follicular thyroid carcinoma three years and one month after thyroidectomy, respectively. The first patient had pulmonary metastases which had a microfollicular pattern closely resembling that of the primary neoplasm. In the second patient, the pulmonary metastases were distinctly more pleomorphic than the primary tumor, whereas the skeletal metastases had a follicular and lobular pattern closely resembling that of the primary thyroid neoplasm.

Autopsies were performed on only two patients who died of anaplastic thyroid carcinoma. In one patient who died of local recurrence five months postoperatively, the recurrent anaplastic neoplasm was identical histologically with the original thyroid carcinoma. The second patient, who died two days postoperatively, had had an epidermoid carcinoma in the primary thyroid neoplasm removed surgically. The residual thyroid neoplasm observed at autopsy had mainly an anaplastic, multinucleated pattern with only minimal epidermoid differentiation. Neoplastic tissue metastatic in mediastinal lymph nodes of this patient had a poorly defined follicular pattern

nomas with a follicular pattern (4, 59) should be regarded and classified as follicular variants of papillary carcinoma. Their cytologic characteristics, age incidence, mode of metastases, clinical course, and survival data clearly indicate their close relationship to papillary carcinoma. Future reports from this laboratory on thyroid carcinoma will include this modification of the basic classification of Warren and Meissner (4), a modification already made by Crile and Hazard (73).

Therapy of Thyroid Carcinoma

The results of the present study indicate that thyroid carcinoma is a lethal disease, and for that reason alone would suggest that, in such a malignant process, radical therapy designed to eradicate the neoplastic tissue is warranted. It is apparent, however, that some forms of the disease, notably papillary carcinoma, may have an extremely long course compatible with prolonged periods of survival without disability, even with residual or recurrent disease. It seems likely that in papillary and follicular carcinoma, at least, long postoperative survival has been credited to certain surgical procedures employed, rather than to the unique biologic nature of these neoplasms.

Although the course of many malignant neoplasms may be unpredictable, modern therapy of cancer aims at early operation and total removal of the neoplastic process This radical surgical treatment as a rule includes removal of the organ in which the neoplasm has originated and wide removal of lymph nodes draining the area of the primary neoplasm, when the process is of epithelial origin In thyroid cancer, this radical therapy would include radical thyroidectomy and radical resection of cervical lymph nodes, both superficial and deep, and possibly of the mediastinal lymph nodes as well Martin (74), at Memorial Hospital in New York, is one of the recent advocates of radical surgical treatment. In the case of thyroid carcinoma, especially the papillary type, some departures have been made from this concept, mainly by Crile (75), for several reasons: 1) many papillary carcinomas occur in young females, and in these patients some surgeons may prefer to perform less radical operative procedures with less scarring and deformity of the neck; 2) many papillary carcinomas grow slowly, and recurrent metastases to cervical lymph nodes apparently can be

irradiation. Experience in animals and human beings strongly implicates irradiation as one of the factors etiologic in thyroid carcinoma (32 to 49).

Histologic Types of Thyroid Carcinoma

There are two basic types of thyroid carcinoma, papillary and follicular. Anaplastic carcinoma probably includes the de-differentiated forms of both papillary and follicular carcinoma. Sloan (13) speculated on the origin of anaplastic carcinomas, and also noted the old-age level at which they generally occur, the frequency of pre-existing tumors suddenly showing rapid growth, and the occasional finding of more differentiated patterns associated with the highly undifferentiated patterns of anaplastic carcinoma These findings have been duplicated in the present study.

It is of interest to compare these anaplastic thyroid carcinomas in the human being with an anaplastic thyroid tumor in the rat induced with thiouracil by Purves and associates (72). Unlike the more differentiated thyroid carcinomas in these animals, the anaplastic tumor was not dependent on TSH, was not inhibited by feeding thyroxine, its growth was not accelerated by thiouracil, and it rapidly killed its host in three weeks to two months. It was concluded by Purves and associates (72) that this anaplastic thyroid carcinoma in the rat was the result of mutations in a dependent thyroid carcinoma and not the result of multiple tumor transplantations.

The present study indicates that a similar relationship exists, in the human, between differentiated thyroid carcinomas, particularly the papillary type, and anaplastic thyroid carcinoma The former, especially papillary carcinoma, occurs in younger individuals, whereas anaplastic carcinoma occurs mainly in persons past 50 years of age. The common finding of long-standing goiter in patients with anaplastic carcinoma and the tendency toward more undifferentiated and anaplastic patterns in thyroid neoplasms observed at autopsy (as compared with the patterns observed in the surgical specimen) also suggest that this anaplastic change occurs over a period of many years. It apparently is dependent upon the age or duration of the neoplastic process rather than upon the age of the patient.

This pathologic study has also shown that some thyroid carci-

form hemithyroidectomy. For localized follicular carcinoma, Crile (76) advocates total lobectomy, and more radical resection of the gland for invasive follicular carcinoma.

In the present study, no localized follicular carcinomas (invasive adenoma) extended to the opposite lobe. Since these neoplasms do not invade lymphatics but do show vascular invasion, total lobectomy and resection of the isthmus seem indicated.

Nineteen invasive follicular carcinomas (21%) did extend to the opposite lobe, and there was local recurrence with less than radical resection in 18 patients (20%). Of the deaths from follicular carcinoma, four (20%) were due to respiratory obstruction resulting from local growth of carcinoma in and about the thyroid region. For these reasons, total thyroidectomy (bilateral total lobectomy) would seem indicated for invasive follicular carcinoma.

For anaplastic carcinoma, Crile (76) advocates radical lobectomy or total thyroidectomy for the medullary type only, since surgery is not curative in the other types. In the present study, the finding of long survival in four patients with small-cell anaplastic carcinoma was surprising and unexpected. For anaplastic carcinomas, other than the giant-cell type, radical total thyroidectomy would appear indicated, since a poor prognosis based on the anaplastic or undifferentiated pattern may be erroneous.

Most of the current controversy in the surgical treatment of thyroid carcinoma revolves about the disposition of cervical lymph nodes in the patient with thyroid carcinoma Martin (74) has described the procedures used at the Memorial Hospital. In any case where carcinoma (all types) is found, even though the cervical nodes are not clinically involved, a radical dissection of cervical lymph nodes on the side of the primary neoplasm is done. Martin stresses the point that this is not a prophylactic neck dissection. This radical disposition of cervical nodes is done 1) because of the high incidence of neoplastic involvement of cervical lymph nodes in patients at Memorial Hospital; and 2) because of the high incidence of venous invasion by thyroid carcinoma and the belief that this venous involvement can be successfully attacked only by block dissection of the cervical tissues. The radical resection, as outlined by Martin, includes the submaxillary and spinal accessory chains of lymph nodes, the sternomastoid muscle, and

treated successfully, at least temporarily, by repeated excision of these involved cervical lymph nodes; and 3) some papillary carcinomas are apparently dependent neoplasms and appear to regress during therapy with thyroid extract.

Most thyroid surgeons agree on the value of immediate pathologic examination with preparation of frozen sections at the time of surgery (31, 74). With a definitive diagnosis of the type of carcinoma present, the operative procedure can be continued accordingly In the case of papillary carcinoma, Martin (74) advocates hemithyroidectomy (total lobectomy) rather than partial lobectomy. If the papillary carcinoma is in or near the isthmus, wide resection of the lateral lobes is done. Crile and associates (76) also advocate hemithyroidectomy (total lobectomy) for localized papillary carcinoma, but if the neoplasm is multicentric, total thyroidectomy with preservation of at least two parathyroid glands is carried out. Underwood and co-workers (31) use hemithyroidectomy (total lobectomy), or wider resection if the isthmus or the other lobe is involved When papillary carcinoma is present in one lobe, total lobectomy is done on that side, and a subtotal lobectomy on the opposite side.

The results of the present study strongly indicate the advisability of radical treatment of a primary papillary carcinoma in the thyroid gland. Of the 180 patients with papillary carcinoma in this study, 30% had extension of the neoplasm from the lobe of origin to the opposite lobe, and often this extension was demonstrable only microscopically There was local recurrence of papillary carcinoma after less than radical operations in 12% of patients.

Since 29% of deaths from papillary carcinoma in this study were due to respiratory obstruction resulting from growth of the neoplasm in and adjacent to the thyroid area, radical removal of the thyroid gland would seem indicated, and this should be done by bilateral total lobectomy Because of the propensity of papillary carcinoma to permeate thyroid lymphatics, subtotal lobectomy on the side opposite the primary lesion would seem an incomplete operation, to be followed possibly by local recurrence. It also seems likely that the neoplasm in the thyroid gland is the source of distant metastases — another valid reason for total thyroidectomy.

For follicular carcinoma, Martin (74) and Crile (76) also per-

ease in lymph nodes in the neck would certainly seem to warrant radical surgical removal.

Since it has been shown that there is no relation between the size of the primary papillary or follicular thyroid neoplasm and the presence or absence of regional lymph node metastases, the presence of a small primary lesion should not preclude radical attack of the cervical lymph nodes.

Involvement of single cervical lymph nodes is extremely uncommon; as a rule, multiple lymph nodes are involved. It is of interest that the involved lymph nodes in individual cases are frequently of approximately the same size, suggesting that metastases in each of a group of lymph nodes may have begun at about the same time. Not infrequently, histologic examination of lymph nodes and of surrounding tissues removed in radical neck dissections show neoplastic tissue invading distended lymphatic channels in areolar tissue between involved cervical lymph nodes. In the tissues examined in the majority of cases in this study, including those of both children and adults, neoplastic tissue was found invading small veins in and adjacent to cervical lymph nodes containing neoplastic thyroid epithelium. This was observed both in papillary and invasive follicular carcinoma. Both lymphatic and venous invasion in these locations occurred with greater frequency adjacent to nodes extensively infiltrated with neoplastic epithelium, particularly when the latter was less differentiated. It seems obvious that simple removal of individual lymph nodes is inadequate treatment for these extra-nodal extensions. These histologic findings would strongly suggest that cervical metastases might well be a source for distant dissemination and distant metastatic lesions through venous invasion.

Other evidence, however, would indicate, as Crile (75) has suggested, that radical resection of cervical lymph nodes in a patient with thyroid carcinoma may be neither necessary nor desirable. Metastatic thyroid carcinoma in cervical lymph nodes *does not* commonly invade adjacent muscle or large cervical veins, although such lesions have been described (74, 77). Continued growth of neoplastic thyroid epithelium in the cervical lymph nodes is not a cause of death from respiratory obstruction. When such obstruction does occur, it results from growth of the neoplasm in and ad-

jugular veins. When bilateral lymph node metastases are evident clinically, total thyroidectomy and bilateral radical neck dissection are done, usually in two procedures. Bilateral neck dissection, however, is not done when there is bilateral neoplastic involvement of the thyroid gland alone without clinically evident bilateral metastases in cervical lymph nodes. Presumably, resection of cervical lymph nodes in patients with follicular and anaplastic carcinoma is carried out in the same fashion.

Crile (75), for reasons listed above, excises groups of involved cervical lymph nodes *en bloc*, preserving the sternomastoid muscle. This procedure is done in patients with papillary, follicular, and the medullary type of anaplastic thyroid carcinoma.

Underwood and associates (31) perform radical dissection of cervical lymph nodes, with or without removal of the sternomastoid muscle and jugular vein, in patients with papillary carcinoma, and state that "a single standard approach which will equally fit all situations does not appear feasible at this time."

Distant metastases of most carcinomas of all types probably originate in the primary neoplasm directly, rather than from local regional metastases in lymph nodes If this fact could be proved in the case of thyroid carcinoma, the disposition of the local regional lymph nodes would be of minor importance

There is considerable evidence indicating the advisability of radical resection of cervical lymph nodes in patients with thyroid carcinoma The high incidence of metastases in regional cervical lymph nodes in all types of thyroid carcinoma warrants wide resection of these nodes if the disease is to be eradicated. In papillary carcinoma, early regional lymph node metastases were found in 44% of patients, and late metastases in cervical lymph nodes in 14%. In follicular carcinoma, 25% of the patients had early and 10% had late regional cervical lymph node metastases Of the patients with anaplastic carcinoma, 52% had early regional lymph node metastases, and 16% had regional lymph node metastases occurring later in the course of the disease In addition, significant numbers of patients in the papillary and anaplastic groups especially, had metastases in contralateral or bilateral cervical lymph nodes. Frazell and Foote (63) found positive cervical lymph nodes in 84% of their radical neck dissections. This high incidence of dis-

longed survival with cervical lymph node metastases was due to the inclusion, in the group of patients with follicular carcinoma, those having the follicular variant of papillary carcinoma. As compared with patients with true invasive follicular carcinoma, longer survival, even with cervical lymph node metastases, would be expected.

These data from the present study indicating the advisability of radical removal of cervical lymph nodes in thyroid carcinoma, particularly of the papillary type, would seem to outweigh those indicating the inadvisability of such radical therapy. Since the incidence of metastases in ipsilateral cervical lymph nodes is so high, radical resection of the ipsilateral nodes appears warranted, even though these nodes are clinically free of metastases. Clinically evident contralateral metastases should also be removed radically Although the incidence of metastases in the contralateral lymph nodes is lower (Table 44), bilateral, radical lymph node resection should be considered, particularly when both thyroid lobes are involved by the neoplasm.

Martin (74), Crile (3), and Underwood and co-workers (31) have claimed good results from the form of therapy which each employs. It remains to be proved whether biologic activity of the neoplasm and the resistance of the host, or the therapy employed is the more important factor in the final outcome of the disease. The present study strongly suggests the advisability of a more radical approach to surgical therapy in males and in patients in older age groups (over 40 years of age), since the data presented indicate that thyroid neoplasms in these groups of patients are more aggressive than in females or in younger individuals.

Evaluation of any form of therapy in thyroid carcinoma would seem to require analysis of larger groups of patients than have been studied so far. Comparison of survival of patients treated with different procedures should include not only those with different types of thyroid carcinoma, but also those in different age groups, and in different stages of the disease (as evidenced by size of the primary tumor), and the presence of extraglandular invasion, cervical lymph nodes, and distant metastases. It is apparent that periods of follow-up of well over 20 years would also be necessary to evaluate carefully the results of any form of therapy for thyroid carcinoma. Perhaps such a study, involving many patients, and with

jacent to the thyroid gland, even though cervical lymph nodes may be simultaneously involved. Crile's (75) experience with metastatic regional lymph nodes is similar.

There is a discrepancy between the age incidence of metastases in regional lymph nodes and of distant metastases, as well as in the age at death from thyroid carcinoma, particularly of the papillary type. It is apparent that distant metastases may occur early in the course of thyroid carcinoma — even early in life — and that clinical evidence of these metastases may not be observed until late in the course of the disease. In these instances it is obvious that the course of the disease would probably not be greatly influenced by removal of cervical lymph nodes involved by thyroid carcinoma.

This study has shown no apparent relationship between the incidence of local and distant metastases from thyroid carcinoma. In other words, the incidence of distant metastases shows no significant differences in patients with or without metastases in cervical lymph nodes This finding would suggest that distant metastases do not originate in cervical lymph nodes involved by thyroid carcinoma. However, it should be noted that most of the patients with metastases in cervical lymph nodes had these nodes removed either by simple or radical surgery. It is possible, therefore, that removal of these involved lymph nodes may have lessened the possibility of metastatic dissemination from them. These involved nodes, however, presumably had been present for varying periods of time prior to operative removal. It is possible that some carcinomas, even of the papillary type, may show greater tendencies toward metastases in regional cervical lymph nodes, whereas other neoplasms, perhaps more aggressive, may have a propensity for vascular dissemination, with resulting distant metastases instead.

The survival data obtained in the present study show no significant differences in survival of patients with papillary carcinoma with or without lymph node metastases demonstrable at the time of the first operation. However, it was found that a higher percentage of patients with follicular carcinoma with cervical lymph node metastases survived 10 years after onset and 20 years after operation as compared with patients with follicular carcinoma without cervical lymph node metastases. It is quite probable that this pro-

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the necessary long follow-up, could only be feasible if done cooperatively, combining the experience of groups of physicians, such as the members of the American Goiter Association (62).

The use of postoperative irradiation of the thyroid area has not been evaluated. Some years ago, Dr. Mayo H. Soley, at the University of California Hospital, preferred to withhold postoperative irradiation until recurrence in the thyroid region, with respiratory obstruction, warranted such therapy. However, a significant number of patients in this study who had residual neoplastic tissue, in the tracheal-esophageal groove or in the tracheal wall, which could not be removed surgically, had received external irradiation of the thyroid area early in the postoperative period, and these patients have remained alive without evidences of disease. It seems reasonable to expect that such residual tissue might be destroyed locally by external irradiation.

Of the 293 patients in the present study, 95 were treated postoperatively with thyroid extract. The dangers of stimulation of thyroid carcinoma by the hypothyroid state induced by thyroidectomy or administration of radioiodine, and the advisability of postoperative therapy with thyroid extract for all patients with thyroid carcinoma have recently been stressed by Crile (3). It should be noted, however, that this postoperative therapy with thyroid extract was employed over 20 years ago by Robertson Ward (78), long before experimental and clinical data indicated that many thyroid carcinomas were dependent neoplasms requiring stimulation by thyrotropic hormone for continued growth.

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